Immunosuppressive therapy in children with steroid-resistant, frequently-relapsing, and steroid-dependent idiopathic nephrotic syndrome: a single center experience

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Abstract

Introduction: Immunosuppressive agents are recommended for the management of children with steroid-resistant (SRNS), frequently-relapsing (FRNS), and steroid-dependent idiopathic nephrotic syndrome (SDNS). This study evaluated the efficacy of immunosuppressive agents in these cases.

Methods: This is a retrospective analysis of the records of 130 pediatric cases recruited from a tertiary-care center over a period of two years. They were divided into two groups: 51 patients with SRNS (Group I) and 79 cases with SDNS and FRNS (Group II). They were treated with immunosuppressive agents in addition to steroids, either as double- or triple-combination therapy. Complete or partial remission was considered a good response.

Results: In group I, the proportions of good response to cyclophosphamide, cyclosporine A, and mycophenolate mofetil were 48.6, 60, and 80%, respectively (p = 0.162). In group II, the resistance rate was significantly higher with levamisole than with cyclophosphamide and azathioprine (p = 0.046). Leukopenia was reported infrequently after the administration of cyclophosphamide or azathioprine. The most serious adverse reaction was to cyclosporine A, which induced nephrotoxicity (6.4%), while no adverse effects related to levamisole were reported. Histopathological diagnoses were available in only 39 patients.

Conclusion: The high potency of cyclosporine with steroids recommends its use in patients with idiopathic SRNS with a normal glomerular filtration rate. Its efficacy is augmented when combined with mycophenolate mofetil. Cyclophosphamide, orally or as intravenous boluses, together with alternate-day steroids, could be a good option outside the peripubertal age. The outcomes of FRNS and SDNS could be improved by encouraging compliance with the use of levamisole.

Keywords: childhood nephrotic syndrome, steroid resistance, steroid dependence, relapse, immunosuppressant

1. Introduction

Idiopathic nephrotic syndrome (INS) is defined by altered permselectivity of the glomerular filter associated with non-specific histological abnormalities of the kidney (1, 2). It is the most common type of nephrotic syndrome (NS) in children worldwide as compared to hereditary or secondary types. Its incidence in Egypt is 88% among nephrotic children, where minimal change nephrotic syndrome (MCNS) is the most prevalent variant followed by focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis (MesPGN) (3). Corticosteroids are the mainstay of treatment; more than 90% of children with INS are steroid sensitive (SSNS) and respond to therapy with remission of proteinuria. Unfortunately, INS follows a relapsing and remitting course in the majority, with 90% relapsing at least once, and up to 60% will progress to frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS). Approximately 10-20% of children with NS will not respond to therapy with corticosteroids and are classified as steroid-resistant (SRNS) (2, 4-6). The underlying histopathology usually affects the course of the disease and the response to treatment (7). MCNS is the main pediatric form of INS
and is usually a benign condition responsive to standard steroids treatment (6, 8). Several reports have been published on the changing trends in the histopathology of NS toward the increasing incidence of FSGS in children (7, 9, 10). Those changes are accompanied by an increase in steroid resistance, as FSGS seems to be strongly related to poor response to corticosteroid therapy with the majority of cases evolving to terminal renal insufficiency within several years (8, 11). Management of these patients who fail to show a remission with steroids (steroid-resistant), those who fail to have a long remission (frequently relapsing), and those who cannot be weaned from steroids (steroid-dependent), is difficult since they are at risk for complications of unremitting nephrotic syndrome and progressive renal disease and at risk of the effects of treatment with immunosuppressive medications or long-term steroid use (12). Hence, a rescue therapy in difficult cases of INS is needed in order to avoid unnecessary exposure to toxic drugs. Currently, an optimal combination of immunosuppressive agents to induce remission and to reduce the undesirable effects of high dose and prolonged administration of drugs is still a challenge (13, 14). The aim of this study was to evaluate the efficacy of immunosuppressive agents in steroid-resistant, frequently-relapsing, and steroid-dependent nephrotic syndrome in children.

2. Material and Methods
2.1. Study design and population
This was a retrospective analysis of the records of children presented over a period of two years, from June 2012 to June 2014, to the pediatric nephrology outpatient clinic at Cairo University Children’s Hospital (CUCH), which is the main tertiary referral center for pediatric nephrology in Egypt. The study was approved by the local Ethics Committee. Informed parental consent was obtained prior to enrolling the children in the study. The study included 130 children having INS with steroid-resistant, steroid-dependent, and frequently-relapsing subtypes, for which they received immunosuppressive treatment. Their age at onset of the disease was more than one and less than 16 years, and they were followed up regularly for two years. Patients with incomplete records, secondary nephrotic syndrome, and congenital or syndromic forms were excluded. The cases were categorized into two groups: Group I, which comprised 51 cases with SRNS, and Group II, which comprised 79 cases with SDNS and FRNS.

2.2. Data collection
The data collected included basic demographic, clinical and laboratory data at initial presentation (age at onset; birth date; gender; weight; height; blood pressure; urine analysis, 24-hour urine protein excretion, complete blood count, serum levels of urea, creatinine, cholesterol, albumin, C3 and C4). Histopathological findings of renal biopsy were recorded. Follow-up data of the progress of the disease were recorded, including remissions or relapses and complications of INS and corticosteroid therapy. Responses to immunosuppressive therapy and their adverse effects were recorded.

2.3. Definitions
The terms used for NS definitions, treatment, and its responses as per the unit protocol were as follows: Nephrotic syndrome comprises heavy proteinuria exceeding 50 mg/kg/day or urine albumin/creatinine ratio > 2, hypoalbuminemia < 2.5 g/dL, hypercholesterolemia, and edema (15). Complete remission was defined as the presence of trace or negative proteinuria on the dipstick method for three consecutive early morning specimens. Partial remission was defined as absence of edema, serum albumin > 2.5 g/dL, and a proteinuria of 1+ or 2+ on the dipstick method. Resistance was defined as 3-4+ proteinuria, serum albumin < 2.5 g/dL, or edema (2, 16). Steroid dependence was defined when there were two consecutive relapses while on alternate day steroids or within 14 days of their discontinuation. Frequent relapses were defined by two or more relapses in six months or more than three relapses in any 12 months (2, 16). Steroid resistance was defined as failure to achieve remission despite daily therapy with oral prednisone at a dose of 2 mg/kg/day for eight weeks or on oral prednisone for four weeks followed by three pulses intravenous methylprednisolone (17). Failure of alternative medication was defined when a patient failed to maintain a long remission for a minimum of six months; had two or more relapses over six months while on treatment with any of these agents, its replacement with an alternative medication should be considered. Cyclophosphamide resistance was defined as a failure to achieve complete or partial remission after 8-12 weeks of treatment at the dosage of 2-2.5 mg/kg/d. Cyclosporine A resistance was defined as the failure to achieve partial or complete remission after three months of treatment (18). Levamisole was considered ineffective and stopped if the child failed to maintain remission for six months or developed two or more relapses while on levamisole and every other day steroids or when steroids could not be totally withdrawn (19).
2.4. Renal biopsy
Histopathological diagnoses were available in only 39 patients. Indications for renal biopsy were SRNS (n = 31), SDNS (n = 7), and FRNS (n = 1). Of the biopsied patients, the age at onset of the disease was > 10 years in two children; four children had a positive family history, and two children were hypertensive. Renal biopsy was justified in all SRNS cases, while it was done in FRNS and SDNS cases on an individual basis considering its risk/benefit value or prior to the introduction of cyclosporine A therapy, as per unit plan. Parental consent was obtained for all cases prior to the procedure.

2.5. Immunosuppressive therapy
In the current study, achieving a complete or partial remission after treatment was considered a good response (20, 21). In addition to steroids, patients were treated with one or more of the following immunosuppressive agents: cyclophosphamide (CPO), cyclosporine A (CsA), mycophenolate mofetil (MMF), azathioprine (Aza), and levamisole (Leva). They were given in either double- or triple-combination therapy. In group I, CPO was used as first line treatment in 33 patients and second line in two patients (six patients were biopsied and 29 refused); CsA was used as a first line in 18 patients and as second-line in seven (all 25 patients were biopsied); MMF was added to the treatment regimen in 10 patients who were resistant to CsA. In group II, CPO was used as first line treatment in 25 patients and second or third line in three patients; CsA was used as first line treatment in four cases and as second or third line in two patients; MMF was used as first line in two cases; azathioprine was used as a first line in eight cases and second or third line in two cases; levamisole was used as first line in 40 patients. CPO was given per oral (PO) with a dose of 2-3 mg/kg/day for 8-12 weeks, or intravenously as a monthly bolus of 500-750/m² for six months. CsA was given PO with a dose of 4-6 mg/kg/day for a minimum of 12 months. MMF was given PO with a dose of 1200 mg/m²/day in two divided doses. Azathioprine was administered PO as a single daily dose of 2 mg/kg for eight weeks. Levamisole was given PO at a dose of 2-2.5 mg/kg/dose twice weekly for 6–24 months.

2.6. Statistical analysis
The data were analyzed using IBM SPSS Advanced Statistics, version 22.0 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean, standard deviation, and range. Qualitative data were expressed as frequency and percentage. The chi-squared test (Fisher’s exact test) was used to examine the relationship between the qualitative variables. For quantitative data, the two groups were compared using the Mann-Whitney test.

3. Results
The demographic, clinical, and laboratory characteristics of the study population at the time of initial presentation are provided in Table 1. As shown in Table 2, the two groups were comparable regarding age at initial presentation (p = 0.614), age at onset (p = 0.391), gender (p = 0.336), positive family history (p = 0.1000), and gross hematuria (p = 0.152). Group I showed a significantly higher frequency of hypertension (p = 0.014), hypocomplementemia, and impaired kidney functions (p < 0.001).

| Table 1. Demographic, clinical, and laboratory characteristics at initial presentation of the study population |
|-----------------|-----------------|
| Variables       | Findings        |
| Age at initial presentation (year) | 4.3 (2.0-14.0) |
| Gender ratio (Male/Female)       | 68/62 (1.1:1.0) |
| Age at onset (year)              | 3.9 (1.2-12.0)  |
| Positive family history; n (%)   | 4 (3.1)         |
| Body weight percentile; n (%)    |                 |
| < 5th centile                 | 5 (3.8)         |
| > 95th centile                | 7 (5.4)         |
| Hemoglobin, gm/dL              | 12.0±1.2        |
| Blood urea, mg/dL              | 34.5 (8.0-140.0) |
| Serum creatinine, mg/dL         | 0.7 (0.1-2.6)   |
| Serum albumin, g/dL             | 1.5 (0.4-2.5)   |
| Urine albumin/creatinine ratio  | 4.6 (0.6-52.2)  |
| Serum cholesterol, mg/dL        | 430 (210-913)   |
| C3, mg/dL                     | 110 (20-180)    |
| C4, mg/dL                     | 29 (8-96)       |
Table 2. Comparison between the characteristics of the studied groups at initial presentation

| Variables                          | Group I (n=51) | Group II (n=79) | Test value | p-value |
|-----------------------------------|---------------|----------------|------------|---------|
| Age at initial presentation (year) | 5.2 (2.0-14.0) | 5.0 (2.3-12.0) | 0.506      | 0.614†  |
| Age at onset (year)               | 4.1 (1.1-12.0) | 3.7 (1.3-10.5) | 0.861      | 0.391†  |
| Gender ratio (Male/Female)        | 24/27         | 44/35          | 0.927      | 0.336   |
| Positive family history           | 1             | 3 (3.8)        | *          | 1.000   |
| Hypertension                      | 24 (47.1)     | 6 (7.6)        | 6.050      | 0.014   |
| Gross hematuria                   | 2 (3.9)       | 0              | *          | 0.152   |
| Hypocomplementemia                | 21 (41.2)     | 3 (3.8)        | 28.766     | < 0.001 |
| Impaired Kidney functions         | 22 (43.1)     | 3 (3.8)        | 30.880     | < 0.001 |

Data are expressed as median (range), frequency (%) or ratio. Analysis by: Chi-square test; † Mann-Whitney test; * Fisher’s exact test

The most frequent histopathological diagnosis for all cases was FSGS and MCNS in 15 cases (38.5%) of each. The median age at onset of the disease is shown in Table 3. Age at onset was comparable in children with FSGS and MCNS (p = 0.217). In group I, the most frequent pathological diagnosis was FSGS in 14 (45.2%) followed by MCNS in 10 (32.2%), while, among group II, it was MCNS in 5 (62.5%) (Table 4). The complications of the disease and/or steroid therapy during follow-up are shown in Table 5.

Table 3. Histopathological diagnosis of biopsied children and its relationship to the median age at onset

| Pathological Diagnosis                      | n (%) | Age at onset (months) |
|---------------------------------------------|-------|-----------------------|
| Minimal change nephrotic syndrome           | 15 (38.5) | 48 (13-84) |
| Focal segmental glomerulosisclerosis        | 15 (38.5) | 50 (15-92) |
| Mesangiproliferative glomerulonephritis     | 4 (10.2)  | 36 (12-75) |
| Membranoproliferative glomerulonephritis    | 4 (10.2)  | 60 (16-144) |
| Membranous glomerulonephritis               | 1 (2.6)   | 65 months          |

Table 4. Histopathological pattern in the studied groups (n = 39)

| Pathological diagnosis                      | Group I (n=31) | Group II (n=8) |
|---------------------------------------------|---------------|---------------|
| Minimal change nephrotic syndrome           | 10 (32.2)     | 5 (62.5)      |
| Focal segmental glomerulosclerosis          | 14 (45.2)     | 1 (12.5)      |
| Mesangiproliferative glomerulonephritis     | 3 (9.7)       | 1 (12.5)      |
| Membranoproliferative glomerulonephritis    | 3 (9.7)       | 1 (12.5)      |
| Membranous glomerulonephritis               | 1 (3.2)       | 0 (0.0)       |

Data are expressed as frequency (%).

Table 5. Complications of idiopathic nephrotic syndrome and/or steroid therapy among the study population during follow-up of the disease

| Variable                      | n   | %   |
|-------------------------------|-----|-----|
| Cushingoid facies             | 130 | 100 |
| Infections                   | 70  | 53.8|
| Hypertension                 | 68  | 52.3|
| Gastric irritation            | 11  | 8.5 |
| Overweight                   | 8   | 6.1 |
| Hyperglycemia                | 6   | 4.6 |
| Growth retardation            | 5   | 3.8 |
| Hypertensive encephalopathy  | 2   | 1.5 |
| Hypertensive retinopathy      | 1   | 0.8 |
| Acute renal failure           | 2   | 1.5 |
| Chronic renal failure         | 1   | 0.8 |
| Intracranial hemorrhage       | 1   | 0.8 |
| Extensive subclavian vein thrombosis | 1 | 0.8 |
Apart from cushingoid facies, the most frequent complications were infections (53.8%) and hypertension (52.3%). The most frequently used immunosuppressive agent (either as first or second line treatment) in group I was CPO in 35 (68.6%), followed by CsA in 25 (49%) and MMF in 10 (19.6%); while in group II, levamisole was used in 40 patients (50.6%), followed by CPO in 28 (35.4%), and azathioprine in 10 (12.7%) (Table 6). Among SRNS patients, the difference in response to the three drugs used was statistically non-significant (p = 0.162) (Table 7). In group II, a significantly higher resistance to treatment was found among levamisole users compared to the other drugs (p = 0.046) (Table 8). Adverse effects related to each of the immunosuppressive drugs used in the study are summarized in Table 9. No adverse effects related to levamisole were reported.

### Table 6. Frequency of use of immunosuppressive agents in the studied groups*

| Drug                  | Group I | Group II |
|-----------------------|---------|----------|
| Cyclophosphamide      | 35 (68.6) | 28 (35.4) |
| Cyclosporine A        | 25 (49.0) | 6 (7.6)   |
| Mycophenolate mofetil | 10 (19.6) | 2 (2.5)   |
| Azathioprine          | 0 (0.0)  | 10 (12.7) |
| Levamisole            | 0 (0.0)  | 40 (50.6) |

Data are expressed as frequency (%). * Numbers of cases receiving the drug as first or second line are expressed.

### Table 7. Response to treatment among steroid-resistant nephrotic patients*

| Patient response            | CPO (n=35) | CsA (n=25) | MMF (n=10) | p-value |
|-----------------------------|------------|------------|------------|---------|
| Complete and partial remission | 17 (48.6) | 15 (60.0) | 8 (80.0)  | 0.162   |
| Resistance                  | 18 (51.4)  | 10 (40.0)  | 2 (20.0)  |         |

Data are expressed as frequency (%). * Numbers of cases receiving the drug as first or second line are expressed. Analysis by: Chi-square test. CPO: cyclophosphamide; CsA: cyclosporine A; MMF: Mycophenolate mofetil.

### Table 8. Response to treatment among steroid-dependent and frequently relapsing nephrotic patients*

| Patient response            | CPO (n=28) | CsA (n=6)  | MMF (n=2)  | Aza (n=10) | Leva (n=40) | p-value |
|-----------------------------|------------|------------|------------|------------|-------------|---------|
| Long remission (6 months)   | 24 (85.7)  | 5 (83.3)   | 1 (50.0)   | 8 (80.0)   | 22 (55.0)   | 0.046   |
| Resistance                  | 4 (14.3)   | 1 (16.7)   | 1 (50.0)   | 2 (20.0)   | 18 (45.0)   |         |

Data are expressed as frequency (%). * Numbers of cases receiving the drug as first or second line are expressed. Analysis by: Fisher’s exact test. CPO: cyclophosphamide; CsA: cyclosporine A; MMF: Mycophenolate mofetil; Aza: azathioprine; Leva: Levamisole.

### Table 9. Adverse effects related to immunosuppressive drugs

| Drug                  | Side effect  | n    | %    | Total (%) |
|-----------------------|--------------|------|------|-----------|
| Cyclophosphamide (n=63) | Leukopenia   | 15   | 23.8 | 17 (27)   |
|                        | Hemorrhagic cystitis | 2   | 3.2  |           |
| Cyclosporine A (n=31)  | Gum hyperplasia | 8   | 25.8 | 19 (61.2) |
|                        | Hirsutism    | 7    | 22.6 |           |
|                        | Nephrotoxicity | 2   | 6.4  |           |
|                        | Hypertension | 2    | 6.4  |           |
| Mycophenolate mofetil (n=12) | Diarrhea | 7   | 58.4 | 12 (100) |
|                        | Nausea      | 3    | 25.0 |           |
|                        | Abdominal pain | 1   | 8.3  |           |
|                        | Cough       | 1    | 8.3  |           |
| Azathioprine (n=10)    | Leukopenia  | 2    | 20.0 | 7 (70)    |
|                        | Diarrhea    | 2    | 20.0 |           |
|                        | Abdominal pain | 2   | 20.0 |           |
|                        | Arthralgia  | 1    | 10.0 |           |

Data are expressed as frequency and percentage (%).
4. Discussion

Traditional and newly-developed immunosuppressive agents used in pediatric NS represent a rich area of research for many authors worldwide. The guidelines of the International Study of Kidney Diseases in Children (ISKDC) are changing in quest of higher potency and less side effects. This work demonstrates the experience of our center regarding their use in the treatment of SRNS, FRNS, and SDNS. In SRNS cases (group I), the most frequent histopathologic subtypes were FSGS in 45.2% and MCNS in 32.2%; MesPGN and MPGN in 9.7% for each; and MGN in 3.2%. The immunosuppressive agents that were used either as the first or second line treatment were CPO in 68.6%, CsA in 49%, and MMF in 19.6%. CsA was used as the first-line drug in 18 patients and as the second-line drug in seven patients. The age range of the 18 patients was 10-14 years, and 14 of them had FSGS. Higher gonadal toxicity anticipated in this peripubertal age, as well as the high probabilities of drug resistance in FSGS may explain its choice as the first-line drug despite its side effects, which include nephrotoxicity and dependence. CsA achieved a 60% remission rate that was further augmented with the addition of MMF to 80%. This was higher than the previous reports: Brandis et al. reported a remission rate of 20% for CsA with higher efficiency when combined with steroids (24% versus 14%) (22); another French study reported a 48% remission rate (23). The present study reported an 80% remission rate for MMF combined with CsA and low-dose prednisone in 10 cases of SRNS, in whom CsA proved failure after three months. Similarly, a 70% remission rate was reported recently by Echeverri et al. and colleagues (24). MMF is not recommended for sole use in steroid-resistant cases; it was reported to induce the reduction of proteinuria with partial remission (21). However, Ulinski et al. reported a 50% remission rate in 2005 (25). More recent studies have reported positive results with decrease in relapse rate, less proteinuria, and steroid-sparing dose without any nephrotoxic effect. It was approved by FDA in 1995 for use in pediatric renal transplantation, SRNS, and SDNS (24, 26). CPO was used more commonly in the SRNS group (68.6%), mainly as a first-line treatment. The age range for the 35 patients was 2.3-8 years, and the prevalent pathology in the six biopsied cases was MCNS in four cases and MesPGN in two cases. Despite the small number of cases that accepted biopsy, it was used due to its less adverse effects compared to CsA. In the current study, the remission rate after CPO was 48.6%; it was used mainly through the oral route; and as intravenous six-pulse doses in only two cases. Kari and Halawani (2010) reported a 25% remission rate in steroid-resistant cases treated with CPO (27). Siegel et al. reported a 50% remission rate in children with MCNS, who changed to be steroid sensitive in their future relapse (28). Other authors have reported CPO failure in inducing remission (29, 30). Also, intravenous pulse CPO proved superior to oral CPO (31), especially when combined with steroids. In FRNS and SDNS cases (Group II), renal histopathology of the eight cases were MCNS (n = 5, 62.5%) and one case each of FSGS, MesPGN, and MGN. Levamisole was the most frequently used drug (50.6%) followed by CPO (35.4 %) and azathioprine (12.7%); CsA (7.6%) and MMF (2.5%) were rarely used in this center for steroid-dependent cases. Levamisole treatment resulted in reducing relapse rate in 55% of cases; it maintained six-month remission after a relapse. Madani et al. evaluated the efficacy of levamisole among 304 children and demonstrated that it was effective in children with both SDNS and FRNS, in line with the current study as the relapse rates were reduced by about one-half (32). Ekambaram et al. (2014) found that it was effective in prolonging remission and reducing relapse rate in 77.3% of SDNS and 80.6% of FRNS in India (19). Being potent and steroid-sparing, cheap, palatable, and with few side effects even when taken for years, makes it the most recommended first-line drug for frequently relapsing and steroid-dependent cases. Drug discontinuation is soon followed by a relapse (British Association Study) (33). Hence, the reduced efficacy in our study could be explained by the limited availability of the drug leading to suboptimal adherence to treatment.

In the present study, CPO treatment resulted in a six-month long remission rate of 85.7%. Its efficacy was previously reported (34, 35), and it is recommended to be combined with steroids (35). Also, a 12-week course was preferred over the 8-week course (two-year relapsing rate of 67% versus 22%, respectively) (36). Some studies reported that CPO is less effective in SDNS than FRNS (37). Chen et al. reported a prolonged remission in 72% of children with SDNS (35). Azathioprine was associated with an 80% six-month long remission rate, which was similar to CPO and CsA. In fact, most controlled studies of children with FRNS or SDNS showed that azathioprine does not reduce the number of children who relapse before 6 months significantly compared to steroids or placebo control groups (38). MMF use in idiopathic SDNS is still questionable, but it was recommended by Echeverri et al. as it reduced the frequency of relapses with reduction of steroid doses without deterioration of the glomerular filtration rate (24). However, in the present study, only two cases received MMF because of the limited experience with the use of this drug in children. The restricted use of CsA and MMF in this unit in FRNS or SDNS compared to levamisole and CPO was attributed to being steroid-sparing with relatively low side effects as well as the high potency of this combination in reducing relapse rates.

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In general, apart from steroid complications, the most prevalent adverse reactions of the immunosuppressive drugs were those reported for MMF and azathioprine. However MMF’s adverse reactions were not serious, GIT-related, and could be managed easily. Leukopenia after CPO or azathioprine treatment was reported infrequently. Therefore, a repeated blood count is indicated for early detection in order to discontinue the drug. The most serious adverse reaction was CsA-nephrotoxicity, as reported in two patients (6.4%); it can be prevented by repeated renal biopsy for early detection. Another study on CsA with steroids (37 cases) reported striae in 29.7%, hypertrichosis in 24.3%, gingival hyperplasia in 13.5%, and cataract in 8.1%. CsA and MMF (23 cases) reported diarrhea in 13.0%, abdominal pain in 17.4%, and mild anemia in 13.0% (26). From the analysis of this work compared to the published studies, one can notice similarities and differences between the reported data, and this may be explained as many of the studies are non-randomized, include a small number of cases, and lack control groups.

5. Conclusions
The high potency of cyclosporine A with steroids recommends its use in patients with idiopathic SRNS provided they have a normal glomerular filtration rate. Its efficacy is further augmented when combined with MMF. This allows the weaning of patients from CsA after induction of remission, keeping them on MMF and low-dose steroids only, thereby avoiding CsA-nephrotoxicity and dependence. Cyclophosphamide as six-monthly intravenous boluses or orally for three months together with alternate-day steroids could be a good option provided that the patient is not within the peripubertal age range. However, deficient pathological data and its infrequent use in the boluses form were limiting factors for its proper assessment. In FRNS and SDNS, outcome could be improved by encouraging compliance with the use of levamisole. Long-term studies as well as the exchange of multi-center data should be encouraged for continuous update of published recommendations and guidelines.

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Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this work and article equally. All authors read and approved the final manuscript.

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