Kidney Medicine

Efficacy and Safety of Immunosuppressive Therapy in Primary Focal Segmental Glomerulosclerosis: A Systematic Review and Meta-analysis

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Rationale & Objective: Focal segmental glomerulosclerosis (FSGS) is a rare condition that can lead to kidney function decline and chronic kidney failure. Immunosuppressants are used to treat primary FSGS. However, their efficacy and safety in FSGS are not clearly established. We assessed current knowledge on clinical effectiveness and safety of immunosuppressants for primary FSGS.

Study Design: Systematic review of randomized controlled trials, interventional nonrandomized controlled trials, observational studies, retrospective studies, and registries.

Setting & Participants: Patients with primary and genetic FSGS.

Selection Criteria for Studies: Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for English-language, primary-FSGS studies from inception to 2019. Clinical outcomes were changes from baseline in proteinuria, kidney function, and kidney survival.

Data Extraction: 2 investigators independently screened studies and extracted data.

Analytical Approach: Study results were summarized using random-effects models either as ratios of means between follow-up and baseline measurements or as HRs.

Results: We included 98 articles. Substantial heterogeneity was observed in patient baseline characteristics and study designs. Most studies assessed treatment with corticosteroids alone or combined with other drugs, mainly immunosuppressants. Patients treated with immunosuppressants showed reduced proteinuria (14 studies; ratio of means, 0.36; 95% CI, 0.20-0.47), decreased creatinine clearance (mean difference, −25.03; 95% CI, −59.33 to −9.27) and (significantly) lower estimated glomerular filtration rates (mean difference, −7.61 mL/min/1.73 m^2; 95% CI, −14.98 to 0.25 mL/min/1.73 m^2). Immunosuppressant therapy had an uncertain effect on reducing the chronic kidney failure risk. Hypertension and infections were the most commonly reported adverse events.

Limitations: Heterogeneity in study designs, patient populations, and treatment regimens; no access to individual patient–level data.

Conclusions: This systematic review supports proteinuria reduction with immunosuppressant therapy in primary FSGS over varying follow-up periods. The effects of immunosuppressants on kidney survival remain uncertain. This review underscores the need for better-designed and adequately controlled studies to assess immunosuppressant therapy in patients with primary FSGS.

Complete author and article information provided before references.

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a rare condition affecting patients of any age, which can lead to decline in kidney function and progression to chronic kidney failure (CKF). FSGS arises as a consequence of multiple pathways either individually or collectively resulting in injury to the podocyte and can be classified into primary, secondary, and genetic forms.[1] Primary FSGS, which is presumably caused by a putative circulating factor that leads to podocyte injury, typically presents with abrupt-onset, severe nephrotic syndrome.[2] Patients with primary FSGS presenting with nephrotic syndrome are usually treated with corticosteroids and other immunosuppressive drugs. Although corticosteroids remain the mainstay of first-line treatment for primary FSGS, more aggressive therapeutic approaches may be taken in patients who relapse or remain persistently nephrotic despite conservative therapy: namely, additional use of or a shift to other immunosuppressive agents, such as calcineurin inhibitors (CNIs), mycophenolate mofetil, or rituximab.[3,4]

Despite general acceptance in clinical practice of their use in the management of primary FSGS, the efficacy and safety of immunosuppressive therapies are not yet clearly established. Several years have passed since the last attempts to qualitatively or quantitatively synthesize the available evidence on the effects of immunosuppressive therapies in patients with primary or idiopathic FSGS,[3,5] highlighting the necessity for an update on this important subject. Therefore, the objective of this systematic literature review was to assess the current knowledge on the clinical effectiveness and safety of immunosuppressants in the treatment of primary FSGS.

METHODS

Search Strategies

A comprehensive search of the peer-reviewed literature was conducted on April 5, 2019, using the Medline (PubMed), Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects), and

PLAIN-LANGUAGE SUMMARY

Focal segmental glomerulosclerosis (FSGS) is a rare condition that damages the kidney and may result in chronic kidney failure. This systematic review examined treatment of primary FSGS with therapies that suppress the immune system (ie, immunosuppressants), including steroids, calcineurin inhibitors, and alkylating agents, in 98 publications (7 were randomized controlled trials). Treatment of FSGS targets the reduction of protein in urine to protect long-term kidney health. On average, protein in urine was reduced by >50% in patients treated with immunosuppressants. The effects on kidney function and kidney survival were uncertain. The most common adverse events during treatment were hypertension and infections. To better understand the effects of immunosuppressant therapies in FSGS, adequately controlled studies are needed.

EMBASE databases. The systematic literature review was structured using the Population, Intervention, Comparator, and Outcomes strategy. Keywords and the respective syntax used in each database are shown in Tables S1-S3. Systematic searches were further supplemented with manual searches to identify additional, relevant studies not retrieved with the systematic literature review protocol or published after the date of the systematic search.

Study Selection

Although randomized controlled trials (RCTs) provide the strongest level of evidence, very few randomized studies investigating the clinical efficacy of immunosuppressants in the treatment of patients with primary or idiopathic FSGS are currently available. Therefore, a broad range of study designs were included in this systematic literature review in addition to RCTs, including interventional non-RCTs (ie, single-arm clinical trials and nonrandomized comparative studies), observational studies, retrospective studies, and registries. Studies were required to meet the following additional criteria to be included in this investigation: (1) report treatment of patients with primary or idiopathic FSGS with any immunosuppressant agent, either with a single arm or in comparison with non-immunosuppressive agents, placebo, or no treatment; (2) describe any of the following efficacy outcomes: proteinuria (as daily proteinuria or the urinary protein-creatinine ratio), kidney function (estimated glomerular filtration rate [eGFR] or creatinine clearance [CrCl]) and survival (CKF, doubling of creatinine, or author-reported survival), and adverse events; (3) be human studies; and (4) be published in English with the full text available. No time limit was applied in this literature search.

The exclusion criteria considered in this systematic literature review were as follows: (1) patients with secondary FSGS; (2) FSGS recurrence after transplantation; (3) immunosuppressive therapy with rituximab or other monoclonal antibodies; (4) animal and in vitro studies; and (5) economic evaluations, editorials, notes, comments or letters, narratives, articles without abstracts or nonsystematic literature reviews, case reports, or case series.

Data Extraction

Studies were independently screened by 2 investigators (BM/MF) who subsequently extracted pertinent data and analyzed the results. Any disagreements or discrepancies in study selection and data collection between the 2 authors were resolved by discussion with a third author (NP).

Daily proteinuria was recorded in g/day or the urinary protein-creatinine ratio. Kidney function was represented as the eGFR or CrCl. Kidney outcomes were recorded as the kidney survival rate, rate of patients reaching CKF, or time to CKF. Treatment-related changes at baseline and follow-up periods were reported as mean values and standard deviations, unless otherwise specified. Whenever the variation was represented as the standard error of the mean, the standard deviation was calculated using the following formula: standard error of the mean × square root of sample size.

Quality Assessment

Risks of bias of randomized clinical trials considered for inclusion in the systematic literature review were assessed independently by 2 authors (BM/MF) using the risk-of-bias checklist developed by the Cochrane Renal Group for RCTs. Discrepancies were resolved by discussion with a third author (AZ). The items assessed in the checklist were allocation concealment; blinding of investigators, participants, outcome assessors and data analysts; the intention-to-treat analysis; and completeness to follow-up. Each item was answered with yes, no, or unclear, in combination with a narrative response and an overall assessment of the risk of bias.

Statistical Analyses

Meta-analyses were performed with R (v. 3.6.0), using the dplyr (0.8.3), meta (4.9.5), and metaphor (2.1.0) packages. The ratio of mean (ROM) values at the last time point reported and of mean values at baseline, as well as their 95% confidence intervals (95% CIs), were calculated for the included studies and transformed into an estimated summary ROM. The ROM was computed using the last time point available for each study. Similarly, the mean differences (MDs) between mean values at the last time point reported and of mean values at baseline, as well as their 95% CIs, were calculated for the included studies and pooled into an estimated summary MD. The standardized MD was computed between treatment and control arms using the last time point reported for both arms. Summary effects of the ROM,

MD, standardized MD, and hazard ratio (HR) were computed using the random-effects model.

RESULTS

Study Selection and Characteristics of the Studies

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart presented in Fig 1 displays the selection process of the articles included in this systematic literature review. The original systematic search retrieved 2,409 articles from the 5 databases, whereas the manual search identified only 1 paper. A total of 2,188 records were assessed for relevance after removal of duplicates. After title and abstract screening, 438 articles were considered for a full-text assessment, and a total of 98 articles were deemed relevant for inclusion in terms of the study population, intervention, and reported outcomes. Among these 98 publications, 33 were eligible for quantitative assessment synthesis and meta-analysis construction.

The 98 publications deemed relevant for inclusion corresponded to 97 independent studies. Most of the included articles were observational studies (n = 85 studies), followed by clinical trials (n = 12 studies), of which 7 were RCTs. A risk-of-bias assessment was performed on the latter studies and, overall, all the included RCTs demonstrated a risk of bias for at least 1 of the 4 potential sources of bias considered in the assessment (Table S4). All studies were conducted in patients with primary or idiopathic FSGS or reported results specifically for this target population. Only 1 study[6] included a subpopulation analysis on patients with genetic FSGS. The age groups of the populations admitted in the studies were nearly equally divided between children or adolescents (n = 45) and adults (n = 43), with 8 studies reporting results for a mixed population of children and adults and 1 study not specifying the ages of the included patients. As expected, the majority of the studies were conducted on patients with nephrotic syndrome, with 4 studies incorporating <50% of patients with nephrotic syndrome and 11 studies in which the nephrotic status was not specified. Some studies evaluated the treatment of naïve patients, whereas others evaluated patients who were steroid resistant (or dependent).

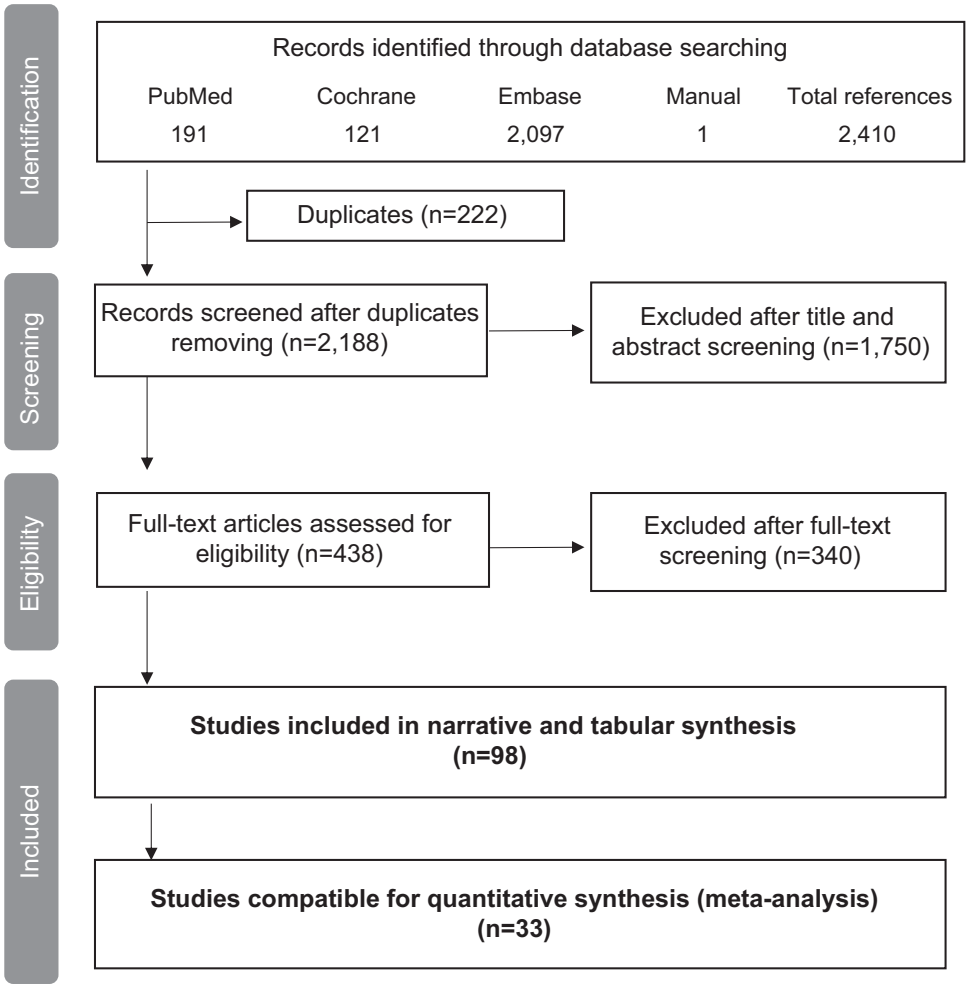

Figure 1. Flowchart describing the study selection process, showing the numbers of studies identified, screened, assessed for eligibility, and included for narrative (tabular) or quantitative (meta-analysis) synthesis.

Various types of immunosuppressive or immunomodulatory drugs were assessed in the studies, including steroids (eg, prednisone, methylprednisolone), CNIs (eg, cyclosporine A and tacrolimus), and alkylating agents (eg, cyclophosphamide). Individual classes of immunosuppressants were used alone (n = 9 studies), in combination with other types of immunosuppressants (n = 82 studies), or in combination with other non-immunosuppressive agents (n = 55 studies). The majority of the extracted literature evaluated the efficacy of steroids in combination with other therapies (n = 78 publications), with only a handful as monotherapy (n = 6 publications). The preponderance of studies focusing on the use of steroids is in alignment with the Kidney Disease: Improving Global Outcome (KDIGO) guidelines,[4] confirming that these agents are the preferred first line of treatment in primary FSGS management. Four studies evaluated the effects of nonsteroid immunosuppressants or immunomodulator agents as monotherapy, namely with cyclosporine (n = 3 studies) and cyclophosphamide (n = 1 study). Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers were the most common control or concomitant therapies. Other non-immunosuppressive concomitant treatments were also reported (eg, other antihypertensive agents, diuretics, statins, antiplatelets), although to a much lesser extent.

Considerable heterogeneity was found among the studies because of different baseline characteristics, patient populations, study designs, treatment regimens, investigated drugs, and time intervals between baseline and follow-up time measurements. The characteristics of the included studies are shown in Table 1.[6-103]

Effect on Proteinuria

Twenty-three studies assessed daily proteinuria after treatment with immunosuppressants, of which 9 studies were excluded in the meta-analysis because of incompatibility of the reported data with this type of analysis (eg, only median values of urine protein were available; variance results were lacking and/or calculation of the standard deviation from the presented data was not possible; or results were only associated with the type of response after immunosuppressive treatment). A ROM meta-analysis was performed with the remaining 14 studies and is depicted in Fig 2.

In patients treated with immunosuppressants, independently of their class, a statistically significant reduction in daily proteinuria of >50% was observed from baseline to the last follow-up measurement (ROM, 0.36; 95% CI, 0.20-0.47; Fig 2). Although the majority of the pooled studies showed a reduction in daily proteinuria, in 2 studies,[7,8] in which patients with primary FSGS received a combination of different immunosuppressants, daily proteinuria values remained unchanged after a follow-up period of 6 months.

Of the 14 pooled studies, only 1 retrospective study[9] evaluated daily proteinuria in patients treated with cyclosporine as a monotherapy, and a 75% reduction in this outcome was reported after a follow-up period of 22.8 months (ROM, 0.25; 95% CI, 0.15-0.42; Fig 2).

A retrospective study[10] assessed the effect on daily proteinuria when children with steroid-dependent or steroid-resistant primary FSGS received cyclosporine in combination with prednisone, in addition to ketoconazole for some patients. Both population subgroups experienced a reduction in daily proteinuria of >50%. This decrease was more pronounced in patients that were steroid dependent (Fig 2).[10]

The majority of the studies included in the meta-analysis had a retrospective design, making it difficult to estimate the effects on daily proteinuria at specific periods of time. However, there were sufficient eligible studies to stratify the results by durations of 6 months (n = 3 studies) and 12 months (n = 4 studies). A more prominent and significant decrease in daily proteinuria was observed at 12 months (ROM, 0.27; 95% CI, 0.16-0.44) when compared with daily proteinuria evaluated at 6 months (ROM, 0.69; 95% CI, 0.41-1.16; Fig S1).

As observed with daily proteinuria, pooling of studies assessing the urinary protein-creatinine ratio after immunosuppressive treatment (n = 7 studies) also demonstrated a decrease of >50% in this outcome from baseline to the follow-up time point (ROM, 0.27; 95% CI, 0.20-0.38; follow-up period ranging from 8-62 months; Fig S2).

Only 1 controlled study[11] estimated the effects of immunosuppressive versus nonimmunosuppressive therapies (prednisone + ACEi and/or angiotensin receptor blockers vs ACEi and/or angiotensin receptor blockers) on daily proteinuria. The last follow-up measurement (12 months) showed that adding immunosuppressants to the treatment regimen led to a stronger reduction in daily proteinuria than ACEi and/or angiotensin receptor blocker monotherapy (MD, −0.41; 95% CI, −0.46 to −0.36; Fig 3). However, in contrast to most primary FSGS studies that look at patients with nephrotic syndrome, this study was conducted in patients with subnephrotic proteinuria (1-3.5 g/24 h).

Effect on Kidney Function

The glomerular filtration rate is the key indicator of kidney function and can be determined with several methods, such as eGFR and CrCl.[104] In this systematic literature review, 20 studies were considered eligible to estimate the MD in the glomerular filtration rate between various follow-up and baseline measurements, using eGFR in 18 studies and CrCl in 2 studies. All studies evaluated the effects of concomitant immunosuppressive therapies, composed of different types of immunosuppressants and/or nonimmunosuppressive medicines.

In studies reporting eGFR, the mean eGFR at baseline was 96.8 mL/min/1.73 m^2, and a statistically significant decrease of 7.61 mL/min/1.73 m^2 was observed after follow-up at any time point (MD, −7.61; 95% CI, −14.98 to −0.25; Fig 4). When the pooled studies were stratified

Table 1. Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Abeyagunawardena et al, 2007[19]	Retrospective	CYC and/or CsA ± chlorambucil ± vincristine (66)	SRNS idiopathic FSGS	<16	100%	—	—	—	—	Follow-up: 10 y	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Prolonged treatment with corticosteroids increases chances of remission and preserves kidney function in patients with idiopathic FSGS; chance of remission may be increased with addition of CYC or vincristine and with prolonged use of low-dose CsA
Abrantes et al, 2006 (Brazil)[20]	Retrospective	Pred ± CYC ± MP ± CsA ± AH (110)	Primary FSGS	<15	100%	—	—	—	—	Follow-up: 10 y	Kidney survival; progression/ time to CKF; HR	At presentation, 3 factors were predictive of CKD: age, creatinine level, and nonresponse to Pred; at kidney biopsy, 4 factors were predictive of CKD: age, percentage of global sclerosis, creatinine level, and presence of hematuria
Abrantes et al, 2006 (Brazil)[21]	Retrospective	Pred ± CYC ± MP ± CsA ± AH (110)	Primary FSGS	<15	100%	—	—	—	—	Follow-up: 10 y	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Long-term overall kidney survival seems to be more favorable in this cohort of FSGS than others
Adhikari et al, 1997 (South Africa)[22]	Prospective	Arm 1: CYC + MP + Pred (7); Arm 2: Shorter CYC + MP + Pred (4)	SR FSGS	<10	83%	—	2.6 ± 1.2; 3.6 + 3.7	63.1 ± 50.9; 97.3 ± 76.9	—	Follow-up: arm 1: mean, 38.1 ± 8.8 mo; arm 2: mean 14.6 ± 11.7 mo; Therapy duration: arm 1: up to 18 mo; arm 2: up to 6 mo	Response to therapy; proteinuria or UP/C; SrCr; eGFR; kidney survival; progression or time to CKF; AEs and/or death	Compared with regimen A, regimen B is 6 times less costly, with a quarter of the number of hospital visits
Adhikari et al, 2001 (South Africa)[23]	Retrospective	CYC ± MP ± CsA ± diuretics ± AH (75)	NS FSGS	<18	100%	—	—	—	—	Follow-up: 2 y or more	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Similar proportion of NS between Black and Indian patients, as well as in kidney outcomes

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Agarwal et al, 1993 (India)[24]	Retrospective	Pred (42)	Idiopathic FSGS	≥14	90.5%	—	—	—	—	Follow-up: 32 ± 7.6 mo	Response to therapy; kidney survival; progression or time to CKF	Steroid responders have better prognoses than nonresponders; Pred should be given an average of 8-12 weeks before categorizing the response
Agrawal et al, 2019 (India)[7]	Retrospective	Arm 1: Tac responsive (Tac + steroids; 7); Arm 2: Tac resistant (Tac + steroids; 7)	SR primary FSGS	≥18	93%	5.5 ± 6.1; 4.9 ± 3.8	—	102.8 ± 25.8 mL/min; 91.6 ± 24.4 mL/min	—	Follow-up: 60 wk; Therapy duration: 48 wk	Proteinuria or UP/C; SrCr; eGFR	Subpodocytic space was preserved in patients on Tac with complete remission and lost in patients with partial response and Tac-resistant cases
Al Salloum, 2004 (Saudi Arabia)[25]	Prospective	Pred + CYC (15)	SR primary FSGS	<12	33%	—	—	—	—	Follow-up: 4 y	Response to therapy; kidney survival; progression or time to CKF	Beneficial therapy for initial SR FSGS remains to be determined, but CYC side effects were negligible
Alexopoulos et al, 2000 (Greece)[26]	Retrospective	Arm 1: Pred ± CsA or CsA ± ACEi (18); Arm 2: Supportive therapy ± ACEi (15)	SR primary FSGS	>15	51%	—	—	—	—	Follow-up: mean, 55 mo (range, 8-142 mo); Therapy duration: mean, 9 mo (range, 6-12 mo)	Response to therapy; SrCr; kidney survival; progression or time to CKF; AEs and/or death	Patients with NS with FSGS may benefit from a more prolonged course of Pred; patients with NS responding to treatment have significantly better kidney survival than nonresponders
Arbus et al, 1982 (Canada)[27]	Retrospective	Steroids ± CYC (51)	NS idiopathic FSGS	<16	100%	—	—	—	—	Follow-up: mean, 10.6 y (range, 2.4-24.0 y)	Response to therapy; kidney survival; progression or time to CKF	Patients with FSGS and NS who go into remission, apparently as a result of steroid or CYC therapy, may become SR within 18 mo and ultimately experience progressive kidney failure
Arias et al, 2011 (Colombia)[16]	Retrospective	Arm 1: FSGS NOS (Steroids, or Steroids + AZA, or CYC, or MMF, or CsA; 196); Arm 2: Tip variant (Steroids, or Steroids + AZA, or CYC, or MMF, or CsA; 37)	Primary FSGS	1-65	97%	—	—	—	—	Follow-up: arm 1: 40 mo (range, 24-132 mo); arm 2: 49 mo (range, 24-87 mo)	Kidney survival; progression or time to CKF; AEs and/or death	The study does not demonstrate a clearly favorable prognosis in a group of patients with FSGS tip variant

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Ayar et al, 2016 (Turkey)[28]	Retrospective	CsA or steroids or CYC or AZA or MMF or ACEi or ARBs (68)	FSGS	≥18	41%	3.62 (range, 0.78-46)	—	65.91 mL/min (range, 15.05-217.13 mL/min)	—	Follow-up: mean, 22 mo (range, 8-76 mo)	Proteinuria or UP/C; eGFR; kidney survival; progression or time to CKF; AEs and/or death	Early diagnosis, follow-up and appropriate immunosuppressive medications affect mortality and clinical progress in primary GN
Bagchi et al, 2016 (India)[29]	Retrospective	Steroids ± CsA or Tac ± CYC or MMF or Rituximab ± ACEi and/or ARBs (116)	Primary FSGS	≥18	100%	5.1 ± 2.6	—	96.9 ± 35.1	—	Follow-up: 23.6 mo (range, 6-65.1 mo)	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death; HR	Patients with steroid resistance have reasonable kidney survival, if proteinuria is reduced with timely use of alternate immunosuppression; CNI resistance is major hurdle in management with limited treatment options
Beşbaş et al, 2010 (Turkey)[30]	Retrospective	Pred ± CYC or CsA ± MP (222)	Primary FSGS	≤16	89.4%	—	12.9 ± 10.9	—	—	Follow-up: 47.9 mo (range, 0.26-270.5 mo)	Response to therapy; kidney survival; progression or time to CKF	Use of immunosuppressive treatment in conjunction with prolonged steroid seems beneficial in children with primary FSGS
Bhimma et al, 2006 (South Africa)[31]	Prospective	Pred + Tac + ACEi + diuretics + CCB (20)	SR idiopathic FSGS	≤16	100%	—	12.5 ± 3.2	117.4 ± 74.0 mL/m^2/min	—	Follow-up after stop of Tac therapy mean, 27.5 mo (range, 13.7-43.7 mo); Tac therapy duration: 12 mo	Response to therapy; proteinuria or UP/C; SrCr; eGFR; AEs and/or death	Tac is a safe and effective treatment for SR FSGS; however, like CsA, some children tend to relapse following cessation of treatment
Brodehl et al, 1988 (Germany)[32]	Prospective	CsA (13)	SRNS FSGS	≤16	100%	10.5 ± 6.8	—	—	—	Follow-up: up to 45 mo; therapy duration: at least 6 mo	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Only half of patients benefited from CsA, so possibly a combination of immunosuppressive drugs could be more effective than CsA alone
Cattran & Rao, 1998 (Canada)[33]	Retrospective	Arm 1: Adults (Pred ± CYC ± AH; 55); Arm 2: Children (Pred ± CYC ± AH; 38)	FSGS	35; 6.0	55%; 76%	—	—	—	90 ± 66; 84 ± 30	Follow-up: 11 y	Response to therapy; Proteinuria or UP/C; CrCl; kidney survival; progression or time to CKF	Steroid treatment beyond 6 months does not appear to be beneficial; CR confers excellent long-term prognosis in children and adults

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Cattran et al, 1999 (USA)[34]	Prospective, single-blind, randomized trial	Arm 1: CsA + Pred ± ACEi and/or ARBs (26); Arm 2: Placebo + Pred ± ACEi and/or ARBs (23)	SRNS FSGS	>18	100%	6.9 ± 3.3; 8.7 ± 4.7	—	—	86 ± 27; 86 ± 31	Follow-up: mean 200 wk	Response to therapy; kidney survival; progression or time to CKF	CsA does not work in every case of FSGS, but a short-term remission to subnephrotic proteinuria was observed in 69% of cases
Cattran et al, 2003 (USA)[13]	Prospective, single-blind, randomized trial	Arm 1: CsA + Pred ± ACEi and/or ARBs (18); Arm 2: Placebo + Pred ± ACEi and/or ARBs (9)	SRNS FSGS	>18	100%	7.2 (range, 3.6-14.4); 9.5 (range, 4-22.4)	—	—	72 ± 24; 66 ± 30	Follow-up: up to 208 wk; therapy duration: 26 wk	Response to therapy; proteinuria or UP/C; SrCr; CrCl	There is no relationship between Palb and outcome, as the antiproteinuric effect of CsA appeared independent of changes in Palb
Cattran et al, 2004 (USA)[35]	Open-label trial	Pred + MMF ± ACEi and/or ARBs (18)	SRNS primary FSGS	≥18	100%	—	9.1 ± 5.2	—	—	Therapy duration mean, 4 mo (range, 3-19 mo)	Response to therapy; proteinuria or UP/C; SrCr; kidney survival; progression or time to CKF	MMF appears safe to use in this group of patients and did lower proteinuria in 44% of this cohort resistant to other forms of treatment
Chávez-Mendoza et al, 2019 (Mexico)[36]	Retrospective	Arm 1: High-dose Pred ± ACEi ± statins (39) Arm 2: First-line CNI (first-line CNI + low-dose Pred ± ACEi ± statins; 11); Arm 3: Rescue CNI first-line high-dose Pred + added CNI rescue for SR disease ± ACEi ± statins; 16)	Primary FSGS	≥18	100%	—	3.7 (IQR, 3.2-7.3); 4.9 (IQR, 3.7-7.6); 5.8 (IQR, 3.6-8.7)	60 (IQR, 41-115 mL/min/y); 58 (IQR, 48-122 mL/min/y); 79 (IQR, 66-112 mL/min/y)	—	Follow-up: 51 mo (IQR, 30-77 mo); CNI therapy duration: 12 mo (range, 6-16 mo)	Response to therapy; eGFR; kidney survival; progression or time to CKF; AEs and/or death	An initial CNI plus low-dose corticosteroid approach in primary FSGS reduces corticosteroid exposure, with a response-to-therapy rate similar to that of the currently recommended high-dose corticosteroid regimen
Chishti et al, 2001 (USA)[12]	Retrospective	Pred + CsA ± ACEi (21)	SR and SD NS FSGS	≤16	100%	—	—	115 ± 36.5	—	Follow-up: mean, 32 mo (range, 12-72 mo); Therapy duration: mean, 20.6 ± 13.7 mo	Response to therapy; eGFR; kidney survival; progression or time to CKF	Single, daily, low-dose CsA appears to be effective for long-term treatment of children with FSGS and NS, with fewer side effects than twice-daily dosing
Choi et al, 2002 (USA)[37]	Retrospective	MMF ± steroids or CsA or AZA + ACEi and/or ARBs (18)	Primary FSGS	≥16	52.9%	—	4.7 ± 5.1	—	—	MMF therapy duration: 8 mo (range, 3-26 mo)	Proteinuria or UP/C; SrCr; eGFR	Empirical MMF therapy in majority of patients with primary GN was well tolerated and achieved the goal of steroid withdrawal, improvement of NS, and stabilization of kidney function

(Continued)

Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Chun et al, 2004 (USA)[38]	Retrospective	Pred ± CsA or CYC (51)	Primary FSGS	>15	75%	7.6 ± 3.7	—	—	—	Follow-up: 73 ± 94 mo; Pred therapy duration: 3.18 ± 1.49 mo	Response to therapy; kidney survival; progression or time to CKF	Patients with NS with primary FSGS should receive a trial of therapy, irrespective of the histologic lesion, when not contraindicated
Crook et al, 2005 (USA)[39]	Retrospective	Steroids ± ACEi and/or ARBs (43)	Primary FSGS	>18	73.6%	8.85 ± 7.2	—	—	—	Follow-up: 46.7 ± 6.6 mo; Steroid therapy duration: 11.7 ± 2.4 mo	Kidney survival; progression or time to CKF; HR	A beneficial effect of steroids was not observed in this predominantly African American adult cohort, as there was no significant association between steroid status and achieving remission of proteinuria
Dumas De La Roque et al, 2018 (France)[40]	Retrospective	Steroids ± CsA ± MMF ± CYC ± ACEi ± ARB ± ACEi + ARB (68)	NS idiopathic FSGS	≥15	100%	6 (IQR, 3.9-9)	—	42.5 (IQR, 29-58)	—	Follow-up: 66 mo (IQR, 30-92 mo); Therapy duration: 15 mo (IQR, 8-36 mo)	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	No predictive factor for relapse was identified by multivariate analysis
Deegens et al, 2005 (Netherlands)[41]	Retrospective	Arm 1: Initially untreated (± ACEi then Pred ± CYC; 20); Arm 2: Treated (Pred; 8)	Primary FSGS	≥18	100%	10.0 ± 5.5; 9.8 ± 3.1	—	—	101 ± 34 mL/min; 123 ± 35 mL/min	Follow-up: Arm 1: 9.4 y (IQR, 2.1-18.6 y); Arm 2: 9.2 y (IQR, 4.0-11.2 y); Therapy duration: Pred: 2.5 ± 0.9 mo CYC: 3 mo	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Case definition using strict clinical criteria identifies a subgroup of patients with idiopathic FSGS who have a good prognosis; in the majority of these patients, immunosuppressive therapy is not warranted unless kidney function deteriorates
Deegens et al, 2008 (the Netherlands)[42]	Retrospective	Arm 1: Treated (Pred or Pred + CYC ± ACEi and/or ARBs; 40); Arm 2: Untreated (± ACEi and/or ARBs; 53)	Primary FSGS	≥18	83%; 49%	10.4 ± 5.8; 5.8 ± 3.7	—	—	—	Follow-up: 66 mo (range, 1-273 mo); Therapy duration: Pred: 5.6 mo (range, 1.3-55.3 mo); CYC: 3 mo (range, 2-12 mo)	Response to therapy; kidney survival; progression or time to CKF; HR	Kidney survival and remission rates were higher in patients with the tip variant
Dhanapriya et al, 2016 (India)[43]	Retrospective	Pred ± CYC ± CsA ± Tac ± MMF (170)	Primary FSGS	≥13	79%	4.26 ± 1.9	—	—	85.8 ± 34 mL/min	Follow-up: 4.32 ± 1.2 y; Pred therapy duration: 6 mo	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Attaining CR significantly improves kidney survival

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Dimkovic et al, 2009 (Serbia & Montenegro)[44]	Retrospective	Steroids + MMF + ACEi ± ARBs or statins (13)	Primary FSGS	≥18	Not specified	5.1 (IQR, 2.7-8.9)	3.26 (IQR, 1.52-7.92)	56.2 ± 33.2 mL/min	—	Follow-up: 12 mo	Response to therapy; proteinuria or UP/C; eGFR	MMF proved to be efficient in 70% of high-risk patients with primary GN, who reached either complete or partial remission without safety concern after 12 months of treatment
Ehrich et al, 2007 (Germany)[6]	Retrospective	MP + CsA + Pred ± MMF or Tac ± ACEis (52)	SRNS idiopathic FSGS	<18	100%	—	—	—	—	Follow-up: 5 ± 3.6 y; Therapy duration: Pred: 24 wk CsA: at least 36 wk	Response to therapy; kidney survival; progression or time to CKF	Combined Pred +CsA therapy including IV-MP pulses resulted in a higher rate of remission when compared with previous reports on using CsA monotherapy or other immunosuppressive combination therapies
El-Husseini et al, 2004 (Egypt)[45]	Retrospective	Arm 1: CsA + ketoconazole ± ACEi (88); Arm 2: CsA ± ACEi (28)	SR or SD primary FSGS	<18	Not specified	6.53; 6.73	—	—	123; 126	Follow-up: 33 mo (range 14-84 mo); Therapy duration: 1-2 y	Response to therapy; proteinuria or UP/C; CrCl; kidney survival; progression or time to CKF; side effects	Coadministration of ketoconazole and CsA in children with idiopathic FSGS is safe; this combination not only reduces the costs but also may improve the response to CsA and stabilize the kidney function
El-Refaey et al, 2007 (USA)[46]	Retrospective	Arm 1: Collapsing FSGS (Pred ± CsA ± MMF + ACEi; 11); Arm 2: Noncollapsing FSGS (Pred ± CsA ± MMF + ACEi; 28)	Idiopathic FSGS	≤17	63.6%; 36%	—	10.8 ± 5.7; 8.6 ± 9.4	96 ± 49; 136.6 ± 65	—	Follow-up: 31.5 ± 22.3 mo; 18.7 ± 12.9 mo	Response to therapy; proteinuria or UP/C; SrCr; eGFR; kidney survival; progression or time to CKF	The outcome of patients with collapsing FSGS at 30 months was better than in previous reports because of stronger immunosuppression or the use of ACEi
El-Refaey et al, 2010 (Egypt)[47]	Retrospective	Pred ± MP ± CsA ± MMF (72)	NS primary FSGS	≤16	100%	3.3 ± 2.8	—	—	—	Follow-up: 76.3 ± 42 mo (range, 9-156 mo)	Response to therapy; kidney survival; progression or time to CKF	Kidney survival is better than in other cohorts
Futrakul et al, 2004 (Thailand)[48]	Retrospective	ACEi + CCB + AP + vitamins E and C ± ARB + Pred (10)	FSGS	Not reported	100%	3.1 ± 4.4	—	35 ± 53.8	34 ± 37.9	Follow-up: ≥10 y	Proteinuria or UP/C; eGFR; CrCl	Therapeutic intervention with multidrug regimens relaxes the arteriolar constriction, thus impacting on the pathogenetic mechanism of kidney disease progression

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Futrakul et al, 2004 (Thailand)[49]	Prospective	Arm 1: Pred + CYC + AH (11); Arm 2: ACEi, ARB, CCB + AP + baby aspirin ± heparin (18)	FSGS	<21	100%	3.2 ± 0.7; 3 ± 0.8	—	60 ± 21; 51 ± 23	47 ± 25; 50 ± 19	Follow-up: 77 ± 24 mo; 97 ± 33 mo	eGFR; BP; kidney survival; progression or time to CKF	In contrast to the therapeutic failure with conventional therapy in Arm 1, clinical improvement in response to the combined formula has been substantiated in all 18 patients in Arm 2
Gellermann et al, 2012 (Germany)[50]	Retrospective, uncontrolled	MP + Pred + CsA ± ACEi and/or ARBs ± diuretics, then MMF (23)	SRNS primary FSGS	<18	100%	—	—	106.2 ± 26.3 (n = 16)	—	Follow-up: 7.0 y (range, 1.7-16.5 y); MMF therapy duration: 3.6 y (range, 0.8-10 y)	Response to therapy; eGFR; AEs and/or death	In children with SRNS or FSGS achieving initial remission, a sequential steroid-free therapy consisting of a combination of CsA and MMF, followed by MMF alone (with the addition of ACEi and ARBs), can provide sustained long-term remission, preservation of kidney function, and better control of BP
Gheissari et al, 2018 (Iran)[51]	Prospective, uncontrolled	Pred + CsA + CYC (26)	FSGS	≤16	Not specified	1.09 ± 1.47	—	—	—	Follow-up: 6 mo	Kidney survival; progression or time to CKF	TRPC6 may be useful for genetic screening in Iranian children with FSGS
Ghiggeri et al, 2004 (Italy)[52]	Open-label, nonrandomized, retrospective	Arm 1: CsA responsive (steroids ± CYC and/or CsA ± MP; 20); Arm 2: CsA intolerant or resistant (steroids ± CYC and/or CsA ± MP; 35); Arm 3: No CsA treatment (84)	SRNS FSGS	<45	100%	—	—	—	—	Follow-up: >2 y Arm 1: 81 (IQR, 4-115); Arm 2: 41 (IQR, 23-92); Arm 3: 48 (IQR, 28-106)	Response to therapy; kidney survival; progression or time to CKF	Long-term CsA (>2 years) has a persistent antiproteinuric effect in the absence of kidney fibrosis
Gipson et al, 2011 (USA)[53]	Open-label, randomized controlled trial	Arm 1: MMF and DEX + Pred + ACEi and/or ARB ± additional AH (66); Arm 2: CsA + Pred + ACEi and/or ARB ± additional AH (72)	SR primary FSGS	2-40	Not specified	—	—	—	—	Follow-up: 78 wk	BP; AEs and/or death	The study did not find a difference in rates of proteinuria remission following 12 months of CsA compared to MMF and DEX in patients with SR FSGS
Gorsane et al, 2016 (Tunisia)[17]	Retrospective	CsA (23)	Idiopathic FSGS	≥16	100%	7.01 ± 4.5	—	—	—	Follow-up: 6.8 ± 3.7 y	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	CsA is effective in treatment of patients with idiopathic FSGS; initial kidney function and CsA resistance are predictive factors of CKF in SR or SD FSGS

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Goumenos et al, 2006 (UK & Greece)[54]	Retrospective	Arm 1: treated (Pred or Pred + AZA or Pred + CsA; 25); Arm 2: untreated (ACEi + CCB + beta-blockers; 26)	Idiopathic FSGS	>18	80%; 50%	5.8 ± 6.6; 4.4 ± 2	—	—	—	Follow-up: 5 y; Therapy duration: 20 ± 6 mo	Response to therapy; kidney survival; progression or time to CKF	Combination of low Pred dose with CsA could be used as initial treatment in patients with higher risk for side effects from the usual Pred dose
Greenwood et al, 2017 (Australia)[55]	Retrospective	Pred ± ACEi and/or ARBs or diuretics (98)	Primary and secondary FSGS	>18	51%	—	—	—	—	Follow-up: 4.32 y (range, 0-17 y)	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death; HR	Concomitant diabetic nephropathy, higher serum creatinine, and lower eGFR at kidney biopsy were associated with poorer kidney prognosis
Gulati et al, 2000 (India)[56]	Prospective	Arm 1: early onset (Pred or Pred + CYC; 36); Arm 2: late onset (Pred or Pred + CYC; 36)	Idiopathic FSGS	≤12 and >12	100%	—	—	92 ± 11; 94 ± 14	—	Follow-up: 14.6 ± 13 mo; 17.8 ± 13 mo	Response to therapy; SrCr; eGFR; kidney survival; progression or time to CKF	Early onset is more often steroid responsive and has a better prognosis than late-onset FSGS
Hari et al, 2001 (India)[18]	Prospective	Arm 1: initial resistance (DEX or MP + CYC; 31); Arm 2: late resistance (DEX or MP + CYC; 34)	SRNS FSGS	≤14	100%	2.6; 3.5	9.7; 10.0	—	—	Follow-up after stoppage of pulse therapy: 25.6 mo (range, 20 mo to 7.3 y); Therapy duration: up to 52 wk	Response to therapy; proteinuria or UP/C; kidney survival; progression or time to CKF; AEs and/or death	Prolonged treatment with IV corticosteroids and oral CYC is beneficial in patients with SR FSGS; although this regimen has considerable side effects, it may prevent chronic kidney failure in a number of patients
Heering et al, 2004 (Germany)[57]	Prospective, randomized	Arm 1: Pred + acetylsalicylic acid ± CsA (34); Arm 2: Pred ± chloroambucil or CsA (23)	Idiopathic FSGS	≥18	100%	5.2 ± 1.1; 4.6 ± 3.1	—	—	—	Follow-up: 4 y; Therapy duration: 2 mo to several y CsA therapy duration: 23 ± 16.5 mo	Response to therapy; proteinuria or UP/C; kidney survival; progression or time to CKF	Additional treatment with chlorambucil was found to be ineffective in FSGS; patients responded to treatment with steroids or CsA
Hogg et al, 2013 (USA)[58]	Post hoc analysis	Arm 1: MMF and DEX + Pred + ACEi and/or ARB ± additional AH (20); Arm 2: CsA + Pred + ACEi and/or ARB (losartan) ± additional AH (22)	SR primary FSGS	7-34	Not specified	—	3.6 (10th-90th percentile, 1.1-9.6); 2.7 (10th-90th percentile, 1.1-5.1)	122.6 ± 50.7; 126.8 ± 50.5	—	Follow-up; CsA or MMF and DEX therapy duration 78 wk; 52 wk	Proteinuria or UP/C; eGFR	The improvement in UP/C after CsA or MMF and DEX was largely sustained for 6 months after therapy; reduction in eGFR in the CsA group was improved 6 months after CsA was stopped, although the levels were lower than baseline in 7 patients who entered the study with decreased eGFR

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Hoseini et al, 2012 (Iran)[59]	Retrospective	CYC ± CsA ± MMF (58)	Primary FSGS	≤18	Not specified	—	—	—	—	Follow-up: 5.7 y (range, 3-20 y)	Kidney survival; progression or time to CKF; AEs and/or death	The study demonstrates an increasing trend in the FSGS incidence in Iranian children; however, kidney survival rates were similar to those reported by others in different countries
Huang et al, 2018 (China)[11]	Prospective, open-label, controlled trial	Arm 1: Pred + ARBs or ACEi (52); Arm 2: ARBs or ACEi (50)	Primary FSGS	>18	No	1.67 (range, 1.04-3.26); 1.58 (range, 1.09-3.43)	—	72.94 ± 28.52 mL/min; 71.33 ± 30.82 mL/min	—	Follow-up: 36 mo (range, 12-101); 37.5 mo (range, 12-117)	Response to therapy; proteinuria or UP/C; AEs and/or death	Additional glucocorticoid therapy is more efficacious compared with ACEi and/or ARBs alone in the treatment of patients with primary FSGS and moderate proteinuria
Inaba et al, 2016 (Japan)[60]	Retrospective	Arm 1: CsA (39); Arm 2: CYC (24)	SRNS idiopathic FSGS	<18	100%	—	—	—	—	Follow-up: Arm 1: 9.0 y (range, 6.3-16.1 y); Arm 2: 14.6 y (range, 10.4-19.0 y); CsA therapy duration until toxicity was found: 4.8 y (range, 2.0-5.8 y)	Response to therapy; kidney survival; progression or time to CKF, AEs and/or death; HR	Therapeutic regimen with CsA could considerably improve both the initial remission rate and the long-term kidney survival rate of children with idiopathic SRNS
Ingulli et al, 1995 (USA)[61]	Prospective	CsA + Pred ± furosemide (21)	SR FSGS	<18	Not specified	6.2 ± 0.2	—	—	—	Follow-up: 8.5 ± 4.7 y; CsA therapy duration: 27.5 ± 22 mo	Proteinuria or UP/C; SrCr; kidney survival; progression or time to CKF; AEs and/or death	Long-term CsA therapy successfully reduces the proteinuria in Black and Hispanic children with SR FSGS and blunts the progression to kidney failure
Jafry et al, 2012 (Pakistan)[62]	Retrospective	Pred ± CYC ± AH (124)	Idiopathic or primary FSGS	≥17	72%	6.0 ± 4.5	—	—	—	Follow-up: 113.6 ± 118.6 wk; Steroid therapy duration: 20.2 ± 7.4 wk	Response to therapy; proteinuria or UP/C; SrCr	Half of adults with primary FSGS achieve sustained remission with steroids and, consequently, exhibit an excellent prognosis for long-term outcome
Jellouli et al, 2016 (Tunisia)[63]	Retrospective	Pred + MP ± CsA or MMF ± CYC (30)	Primary FSGS	≤18	87%	113 ± 87 mg/kg	—	110.5 ± 46	—	Follow-up: at least 1 y; Pred tx duration: 5 mo	Response to therapy; kidney survival; progression or time to ESKD	Children treated with CsA had a high response rate

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Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Kallash & Aviles, 2014 (USA)[64]	Retrospective	Pred + Tac (22)	SRNS primary FSGS	≤17	100%	—	mean, 12.0 (range, 2.2-48.64)	mean, 92.30 (range, 31.3-142)	—	Follow-up: 2.9 y (average, 0.5-7 y)	Response to therapy; eGFR	Tac is a viable option in the treatment of children with idiopathic, SR FSGS; FSGS with nephrotic-range proteinuria should be treated aggressively because even partial remission improves kidney survival
Kambham et al, 2001 (USA)[65]	Retrospective	Steroids ± cytotoxic agents (50, idiopathic FSGS)	Idiopathic FSGS	Mean, 32.6 y	66%	—	—	—	—	Follow-up: 39 mo (range, 1-140 mo)	Kidney survival; progression or time to ESKD	Clinically, ORG is distinguished from idiopathic FSGS by its lower incidence of NS, more benign course, and slower progression to kidney failure
Kangovi et al, 2012 (USA)[66]	Retrospective	Arm 1: CNI, alkilating agents ± ACEi and/or ARBs (32); Arm 2: ACEi and/or ARBs (35)	Primary FSGS	<21	Not specified	—	14.4 ± 11.5; 4.5 ± 6.3	132.9 ± 56.1; 100.8 ± 43.1	—	Follow-up: 70.2 ± 49.5 mo 53.9 ± 28.9 mo; Therapy duration: 11.0 mo; 80.5 mo	Response to therapy; kidney survival; progression or time to CKF; HR	Patients treated initially with RAASi monotherapy may have outcomes that are comparable to or better than those of patients treated with immunosuppression
Kirpekar et al, 2002 (USA)[67]	Retrospective	Arm 1: FSGS with or without mesangial hypercellularity (Pred + MP ± alkylating agent; 10); Arm 2: FSGS plus mesangial proliferation (Pred + MP ± alkylating agent; 15)	SRNS idiopathic FSGS	<18	100%	—	6.1 ± 4.3; 14.9 ± 14.7	—	122.7 ± 100.0; 149.6 ± 79.3	Follow-up: 91.8 ± 55.9 mo; 51.2 ± 33.6 mo; Therapy duration: 17.4 ± 19.4 mo; 9.6 ± 5.8 mo	Response to therapy; kidney survival; progression/ time to CKF	The cause of SRNS cannot be determined by analysis of clinical variables, including age, sex, ethnicity, UP/C ratio, and initial serum creatinine and albumin levels
Klaassen et al, 2015 (Germany)[68]	Retrospective chart review	CsA (23)	SRNS FSGS	≤15	100%	3.4 g/m^2/day (range, 1-55.8 g/m^2/day)	—	—	—	Follow-up: 15.5 y (range, 1.8-27.7 y); CsA therapy duration: 3.1 y (range, 0.5-14 y)	Response to therapy; kidney survival; progression or time to CKF	CNI seems to be justified as a first-line treatment in SRNS; it is successful in many patients and, in our experience, can be stopped successfully in individual patients with CR after treatment

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Korbet et al, 1986 (USA)[69]	Retrospective chart review	Arm 1: Patients with NS (± Pred ± chlorambucil; 29); Arm 2: Patients without NS (no Pred ± chlorambucil; 17)	Primary FSGS	>18	63%	9.47 ± 1.09; 1.64 ± 0.19	—	—	—	Follow-up: 48.0 ± 8.9 mo; 79.9 ± 17.8 mo	SrCr; kidney survival; progression or time to CKF; AEs and/or death	Primary FSGS and nephrotic proteinuria in adults have the same ominous prognostic significance as the similar syndrome previously observed in children; a therapeutic response appears to identify a subgroup among the patients with NS with a better prognosis; when the same glomerular lesion is seen in a patient with nonnephrotic proteinuria, the disease follows a more indolent course
Laurin et al, 2016 (USA)[70]	Retrospective analysis of inception cohort study	Arm 1: Collapsing FSGS (ACEi, ARB, or selective aldosterone blocker ± steroids or CNI; 61); Arm 2: FSGS (ACEi, ARB, or selective aldosterone blocker ± steroids or CNI; 126)	Collapsing and NOS FSGS	Children: ≤15; Adults: >18	58.3%	12.2 (IQR, 5.6-14.8); 4.4 (IQR, 2.3-8.1)	8.9 (IQR, 6.4-15.5); 6.6 (IQR, 2.7-10.1)	48 (IQR, 26-73); 60 (IQR, 42-92)	—	Follow-up: 61 mo (IQR, 17-117 mo); 73 mo (IQR, 24-148 mo); Steroids therapy duration 3.9 mo (IQR, 1.4-6.7 mo); 2.5 mo (IQR, 1.9-6.2 mo); CNI therapy duration 18.2 mo (IQR, 6.1-26.8 mo); 11.5 mo (IQR, 2.9-31.7 mo)	SrCr; kidney survival; progression or time to CKF; HR	Patients with idiopathic, collapsing FSGS present with more severe proteinuria and kidney dysfunction and have overall worse kidney outcomes compared with patients with NOS FSGS; difference in outcomes may be attributable to the baseline severity of disease and possible differences in the decision to treat with immunosuppressive therapy
Laurin et al, 2016 (USA)[71]	Retrospective	Arm 1: no immunosuppressants (183); Arm 2: glucocorticoids alone (173), CNIs ± glucocorticoids (90) other immunosuppressants (AZA, MMF, and CYC; 12)	Primary FSGS	Children: <18; Adults: ≥18	35.6%	3.8 (IQR, 3.5-12); 2.4 (IQR, 1.7-3.3)	—	43.8 (IQR, 27.2-69.9); 62.8 (IQR, 41.7-85.7)	—	Steroids therapy duration: 3.0 mo (IQR, 1.5-5.9 mo); CNI therapy duration: 19.6 mo (IQR, 6.5-34.8 mo)	Kidney survival; progression or time to CKF; HR	Significant association between treatment with immunosuppressive therapy and better kidney survival, despite the fact that patients treated with immunosuppressives tended to have evidence of more severe NS than those who were untreated

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Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Li et al, 2014 (China)[72]	Retrospective	Pred ± Tac ± ACEi and/or ARBs (109)	Primary FSGS	≥14	100%	7.52 ± 2.95	—	100 ± 31	—	Follow-up: 12 mo (range, 6-24 mo)	Proteinuria or UP/C	suPAR is specifically elevated in some patients with FSGS, which differs from the finding in patients with MCD and MN; a suPAR assay may help predict steroid responses in patients with primary FSGS
Lieberman & Tejani, 1996 (USA)[73]	Double blinded, prospectively randomized, placebo controlled	Arm 1: CsA ± CCB (15); Arm 2: Placebo (15)	SR idiopathic FSGS	≤19	Not specified	151.7 ± 162.4 mg/kg/24h; 166.9 ± 137.1 mg/kg/24h	—	103.4 ± 36.7; 86.0 ± 31.3	—	Follow-up: 6 mo	Proteinuria or UP/C; eGFR; kidney survival; progression or time to CKF; AEs and/or death	For patients with SR FSGS, CsA is an additional therapeutic approach for a disease with limited options and a virtually certain progression to CKF
Loeffler et al, 2004 (USA)[15]	Retrospective case series	Tac ± Pred ± ACEi and/or ARBs ± other AH (16; 13 with FSGS)	Treatment-resistant NS FSGS	≤18	100%	—	729.2 ± 419.8	—	217.2 ± 152.3	Follow-up: mean, 6.5 mo (range, 2.5-18 mo); Therapy duration: mean range, 0.4-13 y	Response to therapy; proteinuria or UP/C; CrCl; BP; AEs and/or death	Tac is an effective, well-tolerated medication for treatment-resistant forms of NS in children
Mahmoud et al, 2005 (Egypt)[10]	Retrospective	Arm 1: SDNS FSGS (CsA + Pred ± ketoconazole; 61); Arm 2: SRNS FSGS (CsA + Pred ± ketoconazole; 45)	SDNS + SRNS primary FSGS	≤16	100%	6.7 ± 2.2; 6.6 ± 2	—	—	—	Follow-up; CsA tx duration 12.4 ± 7 mo; 22.6 ± 10 mo; 21 ± 12 mo	Proteinuria or UP/C; SrCr kidney survival; progression or time to CKF; AEs and/or death	Treatment with CsA can be a good therapeutic option in both children with steroid-sensitive or SR FSGS, which may save the toxic effects of long-term, large doses of steroids and improve the control of cases and possibly ameliorate the natural progressive course of the disease
Martinelli et al, 2001 (Brazil)[74]	Prospective	Pred ± CYC (39)	Primary FSGS	≤18	100%	—	—	—	—	Follow-up: 84.6 ± 79.8 mo	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Remission of the proteinuria predicts a good long-term outcome in children with NS and FSGS; the use of immunosuppressive medication in conjunction with Pred seems beneficial in the treatment of SR FSGS

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2	Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient									
			Disease	Age, y	Nephrotic							
Martinelli et al, 2004 (Brazil)[75]	Open-label, nonrandomized, long-term trial	Arm 1: Pred ± ACEi (30); Arm 2: Pred + CYC ± ACEi (24)	NS idiopathic FSGS	24.0 ± 12.0; 14.2 ± 12.1	100%	—	—	—	—	Follow-up: 51.5 ± 59.1 mo; 113.8 ± 88.6 mo	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	CYC in combination with steroids could be a reasonable choice in the treatment of SR FSGS
Mendoza et al, 1990 (USA)[76]	Retrospective	Pred + MP ± CYC or chlorambucil (23)	SRNS FSGS	≤15	100%	—	11.6 ± 7.1	133.5 ± 63.5	—	Follow-up: 45.7 ± 26.6 mo	Proteinuria or UP/C; eGFR; kidney survival; progression or time to CKF; AEs and/or death	This group of children with FSGS has done extremely well following treatment with intravenous MP; the outcome in this retrospective study is significantly better than those in all series we reviewed of children with SR NS and FSGS
Meyrier et al, 1994 (France)[77]	Prospective	CsA ± Pred (36; 14 with FSGS)	NS idiopathic FSGS	≥15	100%	—	—	—	—	Follow-up: 78 mo; CsA therapy duration: 78 mo	Response to therapy; SrCr	FSGS with preexisting, incipient kidney insufficiency and tubulointerstitial lesions should be considered relatively hazardous; a repeat biopsy after a year of treatment is necessary to determine whether treatment can be safely continued or should be stopped; when prolonged remission has been obtained with CsA treatment of more than a year, progressing tapering of the drug to a stop is often followed by stable remission
Mubarak et al, 2010 (Pakistan)[78]	Retrospective	Steroids ± CsA (10)	Idiopathic, collapsing FSGS	≥18	100%	—	—	—	—	Follow-up: 28.7 ± 16.7 mo	Response to therapy; SrCr; kidney survival; progression or time to CKF; AEs and/or death	These preliminary results show that CsA may be effective in the treatment of patients with NS that resist every other form of treatment and especially in the treatment of those with minimal change to lipoid nephrosis

(Continued)

Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Mungan et al, 2015 (Turkey)[79]	Retrospective	Steroids + ACEi and/or ARBs ± cytotoxic agents (20)	Primary FSGS-tip variant	>18	Not specified	5167.35 ± 3975.1	—	—	—	Follow-up: 46 mo (range, 3-137 mo)	Response to therapy; proteinuria or UP/C; SrCr	FSGS-tip variant is a favorable subtype among other FSGS forms; immunosuppressive treatment with steroids that may or may not include cytotoxic agents will resolve proteinuria in the majority of cases
Naseri et al, 2009 (Iran)[80]	Prospective	Pred ± CYC ± CsA (62)	Idiopathic FSGS	<15	Not specified	—	—	—	—	Follow-up mean, 7 y and 2 mo (range, 3 mo-16 mo and 4 mo)	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death	Favorable response to steroid and CYC treatment is a protective factor against disease progression to CKF, and resistance to immunosuppressants implies a poor prognosis
Newman et al, 1976 (USA)[81]	Retrospective	Steroids ± CYC or AZA (33)	FSGS	Children: ≤16 Adults: ≥17	57.6%	—	—	—	—	Not specified	Response to therapy; SrCr; BP; AEs and/or death	FGS in adults represents a more severe and progressive disease process and is less responsive to therapy
Niaudet, 1994 (France)[82]	Prospective	CsA + Pred ± nifedipine and/or acebutolol (20)	SRNS idiopathic FSGS	≤15	100%	—	—	—	—	Follow-up: 45 mo	Response to therapy; kidney survival; progression or time to CKF	CsA, in combination with steroids, is effective in a significant proportion of patients with SR, idiopathic nephrosis
Paik et al, 2007 (South Korea)[83]	Retrospective	Pred ± CYC ± CsA ± MP (92)	SR primary FSGS	≤15	92.4%	—	24.4 ± 25.3	—	—	Follow-up: 98.2 ± 63.3 mo; Therapy duration: MP: 14.2 ± 10.1 mo; CYC and Pred: 2.8 ± 0.8 mo; CsA and Pred: 9.3 ± 6.8 mo	Response to therapy; kidney survival; progression or time to CKF; HR	A more prolonged use of corticosteroid therapy and early introduction of CsA may improve the prognosis for primary FSGS in patients with initial steroid nonresponsiveness
Pei et al, 1987 (Canada)[84]	Prospective	Arm 1: Adults - steroids ± CYC or AZA (55); Arm 2: Children - steroids ± CYC or AZA (38)	Idiopathic FSGS	Children: ≤16; Adults: >16	Not specified	—	—	—	1.5 ± 1.11 mL/second/1.73 m^2; 1.4 ± 0.511 mL/second/1.73 m^2	Follow-up: 59 mo; 64 mo	Kidney survival; progression or time to CKF	All patients with the "typical" lesion of FSGS and idiopathic NS should be treated with a course of steroids, with or without a cytotoxic

(Continued)

Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
												drug, for up to 6 mo; a significant response rate for both adults and children
Ponticelli et al, 1999 (Italy)[85]	Retrospective	Arm 1: Pred ± MP (53); Arm 2: CYC ± AZA ± MP ± Pred ± CsA ± diuretics ± ACEi ± hypolipemics (27)	Primary FSGS	>18	100%	6.96 ± 4.36; 6.58 ± 4.42	—	—	—	Follow-up: 86 mo (range, 12-342 mo); Therapy duration: Pred: 24.5 ± 25.68 wk MP: 19.1 ± 12.34 wk; Other immunosuppressants: 87.1 ± 84.23 wk	Response to therapy; kidney survival; progression or time to CKF; AEs and/or death; HR	~70% of adults with FSGS and NS given prolonged treatment with steroids, immunosuppressive agents, or CsA may still have normal kidney function after 10 y, with a high probability of being without NS
Raja et al, 2016 (India)[8]	Prospective, observational	Arm 1: Collapsing FSGS (Pred ± CYC ± Tac ± rituximab + ARBs; 22); Arm 2: Resistant FSGS (Pred ± CYC ± Tac ± rituximab + ARBs; 19)	Collapsing primary FSGS	≥14	50%; 57.9%	4.6 ± 3.0; 4.5 ± 3.8	—	—	—	Follow-up: 6 to 24 mo	Response to therapy; proteinuria or UP/C; SrCr; kidney survival; progression or time to CKF; AEs and/or death	Cases with collapsing FSGS have a dismal outcome; the prognosis of therapy-resistant, noncollapsing FSGS and collapsing FSGS are similar and lend support to the hypothesis of therapy response being among the most important predictors of progression to CKF
Ramachandran et al, 2014 (India)[86]	Prospective, observational study	Arm 1: Tac responsive (Tac + Pred + ARBs + atorvastatin; 23); Arm 2: Tac resistant (Tac + Pred + ARBs + atorvastatin; 21); Total: All patients (Tac + Pred + ARBs + atorvastatin; 44)	SRNS primary FSGS	≥18	100%	4.57 ± 4.16; 4.57 ± 2.98; 4.57 ± 3.6	—	98.42 ± 22.37; 105.1 ± 21.56; 101.6 ± 24.4	—	Follow-up; Tac tx duration, all patients: 76.64 ± 16.86 wk; 48 wk	Response to therapy; proteinuria or UP/C; SrCr; eGFR; AEs and/or death	Tac is just as effective as any other CNI, but this effectiveness comes at the cost of increased infections, impaired and fasting glucose and diabetes mellitus
Ren et al, 2013 (China)[87]	Prospective, open-label, randomized controlled trial	Arm 1: Pulse CYC + Pred ± ACEi and/or ARBs ± CCB (18); Arm 2: Tac + Pred ± ACEi and/or ARBs ± CCB (15)	SR or SD primary FSGS	>18	100%	3.7 ± 0.5; 4.1 ± 0.5	—	—	—	Follow-up: 12 mo; Therapy duration: 12 mo	Response to therapy; proteinuria or UP/C; SrCr; kidney survival; progression or time to CKF; AEs and/or death	Combination of steroids with either CYC or Tac has similar beneficial effect in treatment of patients with refractory (SD or SR primary) FSGS, as indicated by declined proteinuria, an elevated albumin level in plasma, and stable kidney function; the efficacious effect of Tac is similar to the effect of CYC in a short-term treatment

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Kidney Medicine

Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Rennert et al, 1999 (South Africa)[88]	Prospective	CYC + Pred (10)	SRNS FSGS	6.2 years; ± 3.8 years	100%	—	2.3 ± 2.81	—	—	Follow-up after IVCP: 26 ± 9 mo; IVCP therapy duration: 6 mo	eGFR; AEs and/or death	IV CYC is a valuable adjunctive therapy for children with SRNS and FSGS; remission can be achieved and sustained in the majority of cases, with minimal risk of drug-related side effects
Risler et al, 1996 (Germany)[89]	Prospective	Arm 1: Pred + acetylsalicylate, then CsA (23); Arm 2: Pred ± chlorambucil if no response to corticosteroids, then CsA (24)	Primary GN	>16	100%	5.4 ± 5.2; 3.4 ± 4.9	—	—	—	Follow-up: 36 mo	Proteinuria or UP/C; kidney survival; progression or time to CKF	In some but not all patients with FSGS, CsA can reduce proteinuria
Roberti & Vyas, 2010 (USA)[90]	Retrospective chart review	Tac ± CsA or ACEi, ARBs, or statins (19; 10 with FSGS)	SRNS FSGS	<15	100%	—	7.3 ± 3.7	—	—	Follow-up: mean: 55 mo (range, 17-111 mo)	Response to therapy; proteinuria or UP/C; kidney survival; progression or time to CKF; AEs and/or death	Tac therapy in children with severe NS is well tolerated and initially quite efficacious in achieving remission
Rydel et al, 1995 (USA)[91]	Retrospective	Pred ± cytotoxic agents (81 patients; 30 treated out of 60 patients with NS)	Primary FSGS	35 ± 16	74%	8.1 ± 8.1	—	—	—	Follow-up: 62 ± 75 mo	Response to therapy; kidney survival; progression or time to CKF	Patients with NS with primary FSGS may benefit from a more prolonged course of therapy with Pred
Schwartz et al, 1999 (USA)[92]	Retrospective, clinicopathologic analysis	Arm 1: FSGS-classical segmental scars (Pred; 57); Arm 2: FSGS-cellular lesion (Pred; 43)	Primary FSGS	>18	63%; 91%	4.8 ± 3.6; 12.2 ± 9.8	—	—	—	Follow-up: 75 ± 85 mo; 39 ± 37 mo	Kidney survival; progression or time to CKF; HR	The favorable outcome associated with a remission of proteinuria strongly supports therapeutic intervention in patients with NS with primary FSGS, regardless of the presence of the cellular lesion
Segarra et al, 2002 (Spain)[93]	Noncomparative, open, uncontrolled (prospective)	Pred + Tac + ACEi and/or ARBs ± other AH ± statins (25)	SR idiopathic FSGS	>18	56%	10.3 ± 9.5	—	73 ± 15	—	Follow-up: up to 2 y	Response to therapy; proteinuria or UP/C SrCr; eGFR; CrCl; kidney survival; progression or time to CKF; AEs and/or death	Combined therapy of Tac and steroids induced sustained remission of proteinuria in a significant number of patients with idiopathic focal glomerulosclerosis whose disease was not controlled by the standard therapy of steroids and CsA

(Continued)

Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Segarra et al, 2007 (Spain)[94]	Observational clinical trial	MMF + ACEi and/or ARBs ± other AH ± statins (98; 22 with FSGS)	SR primary FSGS	>18	100%	7.2 ± 3.2	—	67.1 ± 6.3	—	Follow-up: 12 mo; Therapy duration: 12 mo	Response to therapy; proteinuria or UP/C; eGFR; BP	The data do not allow us either to quantify definitively the efficacy of MMF in primary glomerulonephritis that is resistant to other, conventional therapies or to establish solid treatment rules; however, when MMF is prescribed as a rescue treatment, it can cause a moderate reduction of proteinuria in more than half of the patients who do not have other treatment options
Segarra Medrano et al, 2011 (Spain)[95]	Observational study with prospective follow-up	CsA + MMF + ACEi and/or ARBs ± amlodipine and/or furosamide ± statins (27)	Steroid- and CsA-resistant primary FSGS	>18	100%	7.74 ± 3.9	—	88.6 ± 16.5	—	Follow-up: 5 y	Response to therapy; proteinuria or UP/C; eGFR; BP; kidney survival; progression or time to CKF; AEs and/or death	The data from this pilot study show that for patients with CsA-resistant FSGS, treatment combination of CsA and MMF for 12 mo does not significantly modify the evolution of kidney function, although it may induce partial reductions in proteinuria in some patients
Senthil Nayagam et al, 2008 (India)[14]	Randomized, open-label study	Arm 1: MMF + Pred + ACEi and/or ARBs ± other AH ± diuretics ± statins (28; 17 with FSGS); Arm 2: Pred + ACEi and/or ARBs ± other AH ± diuretics ± statins (26; 16 with FSGS)	FSGS	≥18	100%	4.68 ± 1.82 (all patients); 4.95 ± 1.65 (all patients)	—	87 ± 14.2 (FSGS specific); 84 ± 10.1 (FSGS specific)	—	Follow-up: 15.3 mo (range, 12.8-18.2 mo); 16.2 mo (range, 14.5-19.6 mo)	Response to therapy; proteinuria or UP/C; eGFR; AEs and/or death	In the short term, MMF is as effective as a first-line agent as conventional forms of therapy in the management of adults with NS due to FSGS and MN and is well tolerated. MMF-based therapy seems to induce remission faster and reduces exposure to steroids in FSGS

(Continued)

Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Shatat et al, 2007 (USA)[96]	Retrospective review of clinical and biochemical data	CsA ± ACEi (16)	SRNS or SDNS primary FSGS	<18	100%	—	—	130.5 (95% CI, 111.7-144.8)	—	Follow-up while on CsA: 21 mo (range, 8-43.5 mo)	Response to therapy; eGFR	In primary FSGS, steroid resistance may predict CsA resistance; genetic testing for known mutations associated with resistance to immunosuppression may be advisable before treatment of patients with SR FSGS with CsA
Sherali et al, 2010 (Pakistan)[97]	Prospective	CsA + Pred (30)	SDNS + SRNS primary FSGS	<18	100%	—	—	—	—	Follow-up: 12 mo; CsA therapy duration: 12 mo	Response to therapy; SrCr; kidney survival; progression or time to CKF; AEs and/or death	CsA in combination with low-dose, oral Pred was effective in majority of the patients with primary FSGS
Silverstein & Craver, 2007 (USA)[98]	Retrospective analysis	Steroids ± Tac or CsA ± MMF ± ACEi and/or ARBs (41)	SRNS or SSNS primary FSGS	<18	63.4%	—	—	105.4 ± 4.6	—	Follow-up: 3.9 ± 0.5 y (range, 1-17 y)	Response to therapy; eGFR; BP; kidney survival; progression or time to CKF	Impression that more aggressive treatment with CNI, in combination with ACEi and/or ARB or with MMF, may provide a more favorable prognosis for kidney survival in pediatric FSGS
Singh et al, 1999 (USA)[9]	Retrospective	CsA (83; 42 with FSGS)	SRNS FSGS	<18	100%	7.10 ± 7.13	—	—	—	Follow-up: 22.8 mo; CsA therapy duration: at least 8 wk	Response to therapy; proteinuria or UP/C; SrCr; kidney survival; progression or time to CKF; AEs and/or death	CsA showed efficacy in inducing remission in many children with SRNS; whether CsA can prevent progression to CKF in patients with FSGS can only be answered in a large, multicenter trial
Stirling et al, 2005 (UK)[99]	Retrospective record review	Arm 1: Pred ± CYC ± CsA ± AZA (76); Arm 2: untreated (60)	NS primary FSGS	>14	100%	10 (IQR, 6-15); 6.2 (IQR, 5-10)	—	—	—	Pred therapy duration: up to 20 y	Response to therapy; HR	Patients with primary FSGS and nephrotic-range proteinuria, who are treated with corticosteroids, are more likely to enter remission than those who are not treated; remission rates of up to 80% can be achieved with prolonged treatment, and remission is an independent predictor of survival off dialysis; patients who do not achieve remission have a poor prognosis

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Table 1 (Cont'd). Characteristics of All the Studies Included in the Systematic Literature Review for Qualitative Analysis

Study	Study Type	Study Arm (N)	Baseline Characteristics							Follow-Up and/or Therapy Duration	Clinical Outcomes Reported	Main Conclusion of the Study
			Patient			Proteinuria, g/day	UP/C	eGFR, mL/min/1.73 m^2	CrCl, mL/min/1.73 m^2			
			Disease	Age, y	Nephrotic							
Tarshish et al, 1996 (USA)[100]	Prospective, randomized trial	Arm 1: Pred (25); Arm 2: Pred + CYC (35)	SRNS idiopathic FSGS	≤19	100%	161 ± 145 mg/h per m^2; 227 ± 207.06 mg/h per m^2	—	118 ± 42; 109 ± 51.47	—	Follow-up: mean, 44.5 mo; mean, 42.4 mo; range, 3-102 mo	Response to therapy; AEs and/or death	Although 1/4 of the patients underwent CR and another quarter had a decrease in proteinuria, they could not differentiate between spontaneous resolution of the disease and an effect of alternate-day Pred; CYC therapy for children with SR FSGS is not recommended
Troyanov et al, 2005 (Canada)[101]	Retrospective	Pred ± AZA or CsA ± CYC or MMF ± ACEi and/or ARBs (281)	Primary FSGS	>18	68%	—	—	—	73 ± 31	Follow-up: 64 mo (range, 12-346 mo)	Response to therapy; eGFR; BP; kidney survival; progression or time to CKF; AEs and/or death; HR	Achievement and maintenance of PR strongly correlated with both reduction in the rate of kidney disease progression and better kidney survival
Wasilewska & Zoch-Zwierz, 2004 (Poland)[102]	Prospective	Pred + CsA + ACEi (24)	SDNS FSGS	<12	100%	32 ± 19	—	—	133 ± 28	Follow-up: 12 mo; CsA therapy duration: 12 mo	Proteinuria or UP/C; SrCr; CrCl	The urinary TGFβ1 level increases in proportion to proteinuria during relapse of the NS; CsA administration, in combination with an ACEi, causes a systematic reduction in urinary TGFβ1, although the concentration is still higher after 12 mo of therapy than in healthy children
Zagury et al, 2013 (Brazil)[103]	Retrospective	CYC ± CsA + Pred ± MMF (136; 87 with FSGS)	SRNS idiopathic FSGS	<18	100%	—	—	—	—	Follow-up: 6.1 y (0.25-30.83 y)	Kidney survival; progression or time to CKF; AEs and/or death; HR	CsA resistance and FSGS were risk factors for CKF

Note: Unless otherwise specified, data are reported as means ± standard deviations or medians (95% CIs, IQRs, or ranges).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AE, adverse event; AH, antihypertensives; AP, antiplatelets; ARB, angiotensin receptor blockers; AZA, azathioprine; BP, blood pressure; CCB, calcium channel blockers or inhibitors; CI, confidence interval; CKD, chronic kidney disease; CKF, chronic kidney failure; CNI, calcineurin inhibitors; CrCl, creatinine clearance; CR, complete remission; CsA, cyclosporine or cyclosporine A; CYC, cyclophosphamide; DEX, dexamethasone; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephropathy; HR, hazard ratio; IQR, interquartile range; IV, intravenous; IVCP, intravenous pulse cyclophosphamide; MCD, minimal change disease; MMF, mycophenolate mofetil; MN, membranous nephropathy; MP, methylprednisone; NOS, nitric oxide synthase; NS, nephrotic syndrome; ORG, obesity-related glomerulopathy; Palb, albumin permeability; Pred, prednisone or prednisolone; SD, steroid dependent; SDNS, steroid-dependent nephrotic syndrome; SR, steroid resistant; SrCr, serum creatinine; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid sensitive nephrotic syndrome; suPAR, soluble urokinase plasminogen activator receptor; Tac, Tacrolimus; TGFβ1, transforming growth factor β; TRPC6, transient receptor potential cation channel subfamily C member 6; UP/C, urinary protein-creatinine.

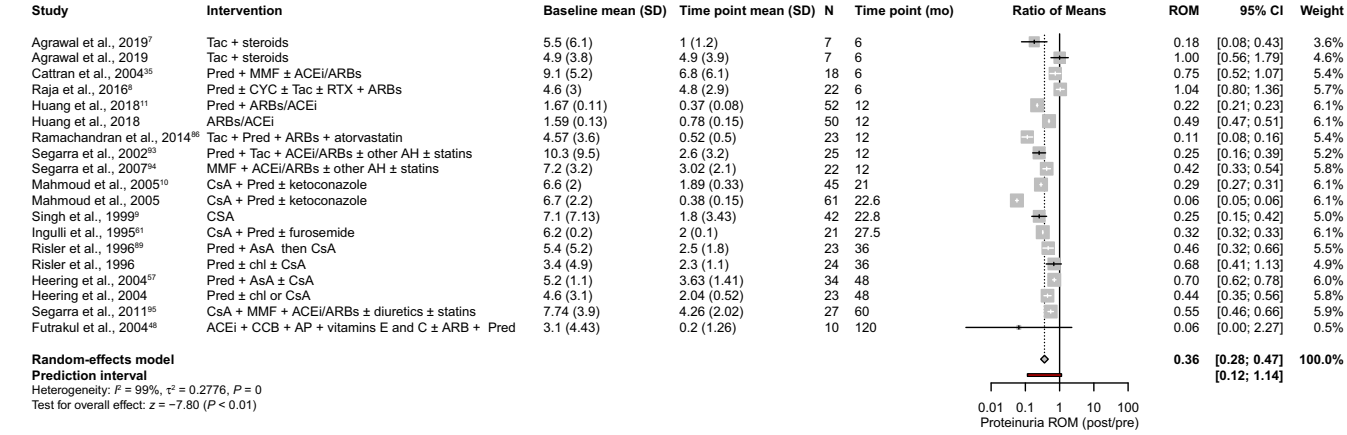

Figure 2. Changes in daily proteinuria outcomes in patients treated with immunosuppressants. Changes in daily proteinuria are expressed as the ratio of means (response ratio) between measurements from the last time point reported and baseline. Study arms with the same treatment within 1 study were included if they corresponded to different patient populations. In Agrawal et al[7] the patients were tacrolimus responsive (first arm in the figure) and tacrolimus resistant (second arm in the figure); in Mahmoud et al[10] the patients had SRNS (first arm in the figure, arm 2 in Table 1) and SDNS (second arm in the figure, arm 1 in Table 1). The summary effect of all studies, regardless of the type of immunosuppressant therapy, is highlighted in bold. Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AH, antihypertensives; AP, antiplatelets; ARB, angiotensin receptor blockers; AsA, acetylsalicylate; CCB, calcium channel blockers; chl, chloramphenicol; CI, confidence interval; CsA, cyclosporine A; CYC, cyclophosphamide; MMF, mycophenolate mofetil; Pred, prednisone; ROM, ratio of means; RTX, rituximab; SD, standard deviation; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; Tac, tacrolimus.

by length of the follow-up period or time point, statistically significant reductions in the eGFR were observed after various months of follow-up (eg, 6, 18, 31, 38, and 60 months; Figs S3 and S4). However, there was no clear correlation between the length of follow-up and the observed effect size.

One study[12] measured eGFR values from baseline to follow-up in patients with primary FSGS that were both steroid-dependent and steroid-resistant, after they received low-dose cyclosporine, prednisone, and, in certain patients, ACEi. Although a statistical comparison of these 2 patient subgroups was not performed by the authors, an increase in eGFR was observed in patients that were steroid dependent, whereas those that were steroid resistant experienced a reduction in kidney function from baseline to follow-up.

Only 2 controlled studies were eligible for inclusion in a meta-analysis to estimate the effects on eGFR of immunosuppressive treatments versus control.[13,14] Both trials demonstrated suboptimal quality, because no allocation concealment and blinding of investigators was practiced. However, in both trials the investigated arms were comparable for treatment completion and were followed for an equal length of time, and in Cattran et al[13] participants were blinded to treatment allocation. The standardized MD meta-analysis results showed that concomitant use of nonsteroid (mycophenolate mofetil in Senthil Nayagam et al[14] or cyclosporine in Cattran et al[13]) and steroid (prednisolone) drugs as immunosuppressant treatment had uncertain or inconclusive effects on the glomerular filtration rate when compared with the use of steroids alone (Fig 5).

In the 2 studies assessing the effect of immunosuppressive treatment on CrCl,[13,15] a statistically significant reduction of 25.0 mL/min/1.73 m^2 (MD, −25.03; 95% CI, −59.33 to −9.27) was observed at the last follow-up in relation to a mean baseline value of 144.6 mL/min/1.73 m^2 (Fig 6). The significant decline in CrCl should be interpreted with caution because of the high mean CrCl value at baseline, suggesting possible hyperfiltration in some patients, as well as the possibility of natural disease progression.

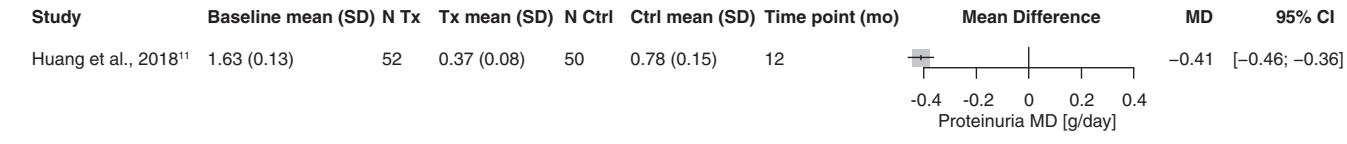

Figure 3. Comparison of immunosuppressive treatment versus nonimmunosuppressive treatment on daily proteinuria. The treatment effect is expressed as the MD between the intervention and control arms at the last time point (prednisone + ACEi and/or ARBs vs ACEi and/or ARBs alone). Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CI, confidence interval; Ctrl, control; MD, mean difference; SD, standard deviation; Tx, therapy.

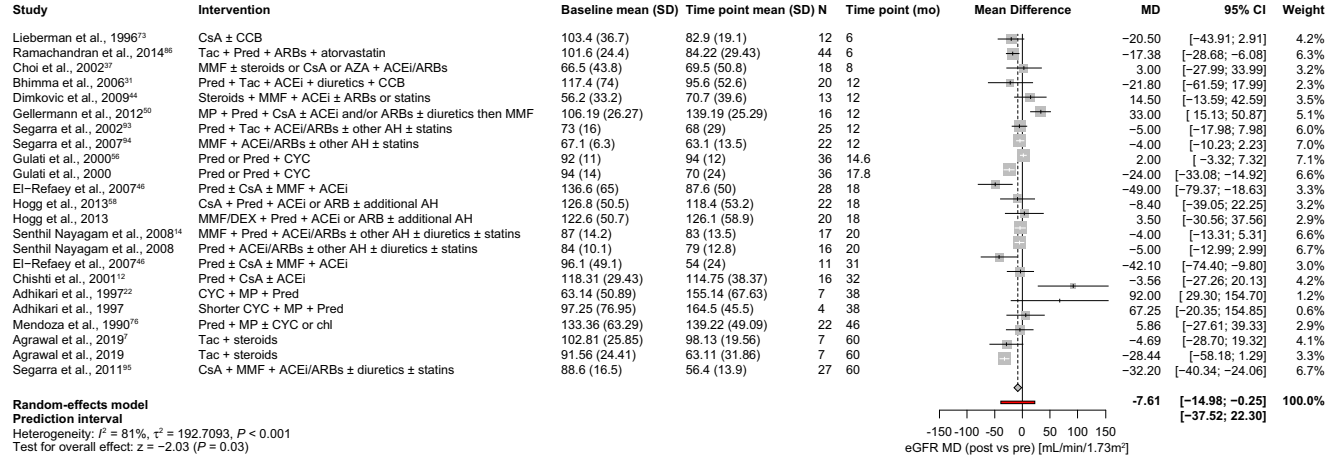

Figure 4. Changes in eGFR in patients treated with immunosuppressants. Changes in eGFR are expressed as MDs between measurements at the last time point and baseline. Study arms with the same treatment within 1 study were included if they corresponded to different patient populations. In Agrawal et al[7] the patients were tacrolimus responsive (first arm in the figure) and tacrolimus resistant (second arm in the figure); in Gulati et al,[56] there were patients with early onset (first arm in the figure) and late-onset (second arm in the figure) of idiopathic FSGS. The summary effect of all studies, regardless of the type of immunosuppressant therapy, is highlighted in bold. Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AH, antihypertensives; ARB, angiotensin receptor blockers; AZA, azathioprine; CCB, calcium channel blockers; chl, chloramphenicol; CI, confidence interval; CsA, cyclosporine A; CYC, cyclophosphamide; DEX, dexamethasone; FSGS, focal segmental glomerulosclerosis; eGFR, estimated glomerular filtration rate; MD, mean difference; MMF, mycophenolate mofetil; MP, methylprednisolone; Pred, prednisone; SD, standard deviation; Tac, tacrolimus.

Kidney Survival

Only 4 retrospective studies reported the HRs of reaching CKF for the use of immunosuppressive medications as a categorical variable (exposure to immunosuppressant treatment vs no exposure). Although these studies used the same measure to determine the impacts of immunosuppressants on kidney survival outcomes, they also showed considerable degrees of heterogeneity in patient populations and treatment regimens. Therefore, the pooled effect of immunosuppressive treatment on kidney survival, when defined as the risk of reaching CKF, was judged to be inconclusive (Fig 7).

Safety and Tolerability

Forty-six out of the 98 included studies showed safety and tolerability outcomes potentially related to the use of immunosuppressants, either as monotherapy or in combination with other immunosuppressant or nonimmunosuppressant medications. Hypertension (n = 21 studies) and infections (n = 20 studies) were the most frequently described adverse events in all patient cohorts. When these events were considered by the authors as treatment related, a higher association was observed with CNI monotherapy treatment than with other classes of immunosuppressants. Death was reported in 20 studies evaluating a variety of immunosuppressant treatment regimens, with only 1 study reporting steroid-related deaths due to sepsis in 2 patients,[16] and another study reporting the death of 1 patient when receiving cyclosporine monotherapy.[17] Other mortality events were not associated with treatment. Hyperkalemia was only reported in 1 study,[18] in 18.6% of patients that were steroid resistant, nephrotic, and had primary FSGS, who were treated with dexamethasone or methylprednisolone in combination with cyclophosphamide. Other side effects, such as hospitalization, were not common among the different treatment cohorts, and could not be associated with a specific immunosuppressive therapy.

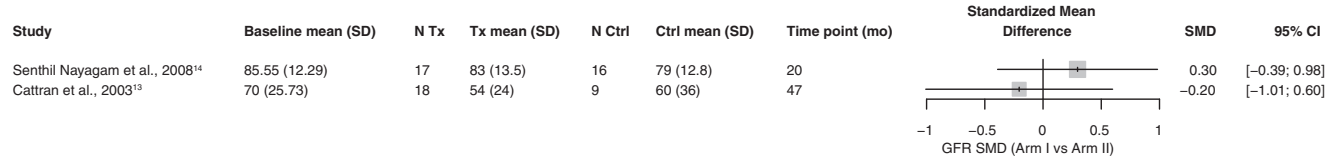

Figure 5. Comparison of the effects of combinations of immunosuppressive treatments (nonsteroid + prednisone vs prednisone alone) on GFR (any measurement). The treatment effect is expressed as the SMD between the intervention and control arms at the last time point. Abbreviations: CI, confidence interval; Ctrl, control; GFR, glomerular filtration rate; MD, mean difference; SMD, standardized mean difference; Tx, therapy.

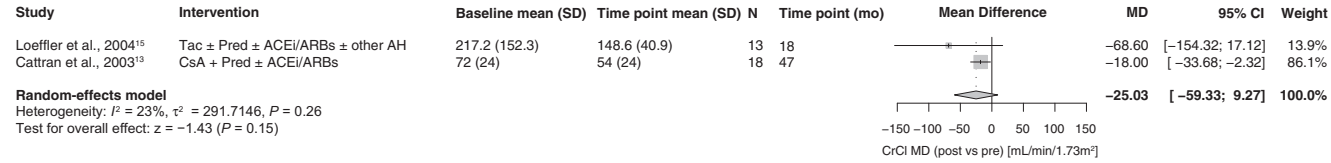

Figure 6. Changes in CrCl in patients treated with immunosuppressants. Changes in CrCl are expressed as the MD between measurements at the last time point and baseline. The summary effect of all studies, regardless of the type of immunosuppressant therapy, is highlighted in bold. Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; AH, antihypertensives; ARB, angiotensin receptor blockers; CI, confidence interval; CrCl, creatinine clearance; CsA, cyclosporine A; MD, mean difference; Pred, prednisone; SD, standard deviation; Tac, tacrolimus.

DISCUSSION

FSGS is a histologic pattern of glomerular injury resulting from heterogeneous clinicopathology entities, and can lead to declines in kidney function and progression to CKF. Steroids and other immunosuppressive drugs are often used to treat patients with primary FSGS suffering from nephrotic syndrome. We have performed a systematic literature review and meta-analysis aimed at assessing the clinical effectiveness and safety of immunosuppressants in the treatment of primary FSGS.

This systematic literature review demonstrates that patients treated with immunosuppressants experienced, on average, decreases in proteinuria from baseline to varying follow-up time points. The effect was more pronounced with longer treatment periods, suggesting that immunosuppressive therapy should be given for at least 6-12 months. Multiple immunosuppressant regimens were evaluated, with the majority of studies (8 of 14) assessing the combination of CNI and corticosteroids. The studies in this analysis include pediatric (n = 3 studies), adult (n = 8 studies), and mixed adult and pediatric (n = 3 studies) populations. Only 1 study (Huang et al[11]) compared renin-angiotensin system blockade alone to corticosteroid therapy. Interpretation of this study is limited, as it only included patients with subnephrotic levels of proteinuria, which is uncommon in primary FSGS. Because of the significant heterogeneity observed among studies and the lack of properly controlled studies, it is difficult to determine how much of the observed effect can be attributed to immunosuppressive treatment. There is a need for more data on potential therapies for primary FSGS, including rituximab and other monoclonal antibodies, which have not been studied in controlled trials in this population.

The effects of immunosuppression on eGFR, CrCl, and kidney survival are uncertain or inconclusive because of high degrees of variability among available studies. The impacts of immunosuppressive treatment on kidney function may require administration of the drugs for longer periods of time than the durations of the studies included in this systematic literature review.

In addition, the safety and tolerability data were limited in the available studies. The most common adverse events included infection and hypertension. Surprisingly, there was very limited reporting of hyperkalemia, which is a well-known side effect of CNIs, especially when combined with renin-angiotensin-aldosterone system blockade. Given the variability in study designs, it is unclear whether hyperkalemia did not occur or whether it was underreported.

Finally, all evaluated studies purportedly included patients with "idiopathic" or "primary" FSGS. The determination of primary FSGS is not well defined, in part because of the lack of measurable biomarkers to distinguish primary from secondary FSGS. The 2021 KDIGO glomerular disease guidelines use more stringent criteria for primary FSGS in adults (proteinuria >3.5 g/day plus serum albumin <30 g/L; with or without edema; the presence of diffuse foot process effacement on biopsy; and no secondary cause identified).[4] Evaluation of immunosuppressive therapy in RCTs with enrollment based on delineation of the underlying pathophysiologic mechanism of disease may have a higher likelihood of demonstrating beneficial

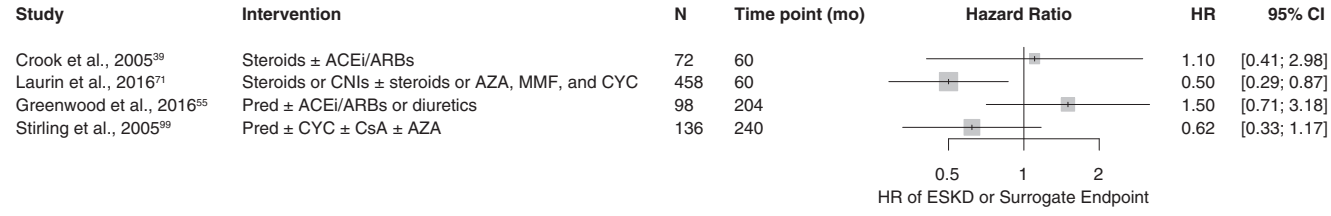

Figure 7. Effects of immunosuppressive treatments on the risk of reaching CKF (or a surrogate end point), assessed using the univariate HR. The risk of reaching CKF (or surrogate end point) is expressed as the HR. Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AZA, azathioprine; CI, confidence interval; CKF, chronic kidney failure; CNI, calcineurin inhibitor; CsA, cyclosporine A; CYC, cyclophosphamide; ESKD, end-stage kidney disease; HR, hazard ratio; MMF, mycophenolate mofetil; Pred, prednisone.

outcomes. In addition to distinguishing primary FSGS and secondary FSGS, screening for and identification of genetic causes of FSGS are needed for accurate evaluation of beneficial treatments for patients with different forms of FSGS and optimal clinical management.

Knowledge of a patient's form of genetic FSGS has implications for individualized treatment, as responses to therapy, such as glucocorticoid sensitivity, resistance to immunosuppression, and potential response to CNIs, have been associated with some genes.[1,105] Genetic testing using the most recent, large gene panels or whole-exon sequencing can be used to identify pathogenic mutations in genes that result in high-penetrance genetic FSGS, as well as *APOL1* risk allele–associated FSGS in patients with sub-Saharan African ancestry.[1,105] In the studies reviewed in the current systematic literature review, just 1 study examined a subpopulation of genetic FSGS. In the absence of genetic screening, it is likely that some patients with unrecognized genetic FSGS were included among the intended patients with primary FSGS, which may have led to misinterpretation of treatment responses in primary FSGS. Further controlled studies are needed to systematically examine different types of genetic FSGS and responses to therapies.

In conclusion, this systematic literature review highlights the limited evidence currently available in the literature and the need for better-designed, adequately controlled studies to reliably assess the effects of immunosuppressants on patients with primary FSGS and to evaluate the safety and tolerability of these treatments. It also underscores the need for clarity in the definition of "primary" FSGS. RCTs with clear entry criteria to identify patients with primary FSGS are needed to adequately evaluate immunosuppressive regimens in the treatment of primary FSGS.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Change in daily proteinuria in patients treated with immunosuppressants, stratified by timepoint

Figure S2. Change in UP/C ratio in patients treated with immunosuppressants

Figure S3. Change in eGFR in patients treated with immunosuppressants stratified by timepoint

Figure S4. Correlation between the last reported follow-up timepoint and the eGFR mean difference from baseline to last reported follow-up timepoint

Table S1. Systematic literature review protocol for PubMed search

Table S2. Systematic literature review protocol for EMBASE search

Table S3. Systematic literature review protocol for Cochrane search

Table S4. Bias assessment for RCTs included in the SLR.

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