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Efficacy and Safety of Immunosuppressive Therapy in Primary FSGS: A Systematic Review and Meta-analysis

Dawn Caster[1], Barbara Magalhaes[2], Natali Pennese[2], Andrea Zaffalon[2], Marina Faiella[2], Kirk N. Campbell[3], Jai Radhakrishnan[4], Vladmir Tesar[5], Howard Trachtman[6]

[1]University of Louisville School of Medicine, Louisville, KY, USA; [2]LatticePOINT, Geneva, Switzerland; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Columbia University Medical Center, New York, NY, USA; [5]Charles University, General University Hospital, Prague, Czech Republic; [6]NYU School of Medicine, NYU Langone Medical Center, New York, NY, USA

Background

Focal segmental glomerulosclerosis (FSGS) is a rare condition affecting subjects of any age, which can lead to decline in renal function and progression to end-stage renal disease (ESRD). Patients with primary FSGS who suffer from nephrotic syndrome are usually treated with steroids and other immunosuppressive drugs. While corticosteroids remain the mainstay of treatment for primary FSGS, a more aggressive therapeutic approach may be taken in patients who remain persistently nephrotic despite conservative therapy, with immunosuppressive agents such as calcineurin inhibitors (CNI), mycophenolate mophetil (MMF), or rituximab reserved for those patients who do not respond to initial treatment with steroids or those who become steroid dependent (Braun et al., 2008; KDIGO, 2012). Despite general acceptance in clinical practice of their use in the management of primary FSGS, the efficacy and safety of immunosuppressive therapies is not yet clearly established.

Aims and Objectives

The objective of this work was to assess the current knowledge on the clinical effectiveness and safety of immunosuppressive therapies in the treatment of primary FSGS.

Methodology

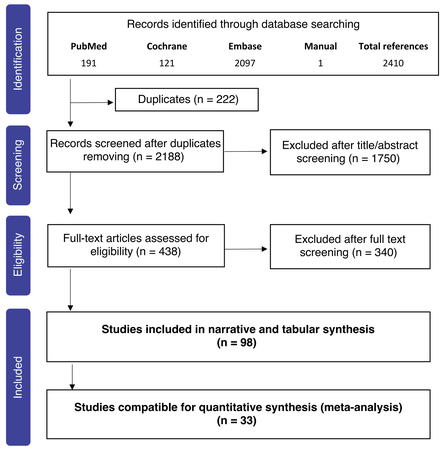
- A comprehensive search of the peer-reviewed literature was conducted on April 5, 2019 using the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases and was complemented with manual search of relevant publications not detected with the systematic literature review (SLR) protocol
- A broad range of study designs and type of publications reporting the treatment of primary or idiopathic FSGS patients with any immunosuppressant agent were included in this SLR. Additional inclusion criteria consisted of: assessment of the main efficacy outcomes (proteinuria, renal function, renal survival, and adverse events), human studies, in English, and with full-text available.
- 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 random effect model was used to compute the estimated summary ratio of means (ROM) between last follow-up timepoint and baseline, the estimated summary mean difference (MD) or standardized mean differences (SMD) between mean values at the last follow-up and baseline, or between the treatment and control arm at the last follow-up timepoint. SMD was carried out by dividing the difference of means by the within timepoints or within-groups standard deviation.

Results and Findings

Study selection and characteristics of the studies

- A PRISMA chart presented in **Figure 1** displays the selection process of the articles included in this SLR
- All studies were conducted in primary or idiopathic FSGS patients, or comprised specific results for this target population. Studies included both pediatric and adult FSGS patients.
- Most of the studies were on nephrotic patients or comprised more than 50% of patients with nephrotic syndrome
- Various types of immunosuppressive interventions were assessed in the studies: steroids (eg, prednisone, methylprednisolone), calcineurin inhibitors (eg, cyclosporine A and tacrolimus), and alkylating agents (eg, cyclophosphamide), among others
- Among the included studies, the majority of immunosuppressive regimens administered to patients consisted of combinations of different types of immunosuppressants (n=83, 83.7%), while a minority used a single type of immunosuppressant (n=9, 9.2%) as monotherapy, with steroids being the most commonly reported treatment agent. Of note, more than half of the studies evaluated the use of immunosuppressive regimens in combination with other non-immunosuppressive agents (n=56, 57.1%)
- A considerable heterogeneity was found among the studies due to different baseline characteristics, patient populations, study designs, treatment regimens, investigated drugs, and time interval between baseline and follow-up time measurements

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



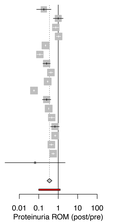
Effect on daily proteinuria

- 23 studies assessed daily proteinuria after treatment with immunosuppressants, of which 9 studies were excluded from the meta-analysis due to 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). A ROM meta-analysis was performed with the remaining 14 studies.

Figure 2. Change in daily proteinuria outcome in patients treated with immunosuppressants.

Study	Intervention	Baseline mean (sd)	Timepoint mean (sd)	N	Timepoint (mo)	ROM	95%–CI	Weight
Agrawal et al., 2019	Tac + steroids	5.5 (6.1)	1 (1.2)	7	6	0.18	[0.08; 0.43]	4.1%
Agrawal et al., 2019	Tac + steroids	4.9 (3.8)	4.9 (3.9)	7	6	1.00	[0.56; 1.79]	5.1%
Cattran et al., 2004	Pred + MMF +/– ACEi/ARBs	9.1 (5.2)	6.8 (6.1)	18	6	0.75	[0.52; 1.07]	5.8%
Raja et al., 2016	Pred +/– CYC +/– Tac +/– RTX + ARBs	4.6 (3)	4.8 (2.9)	22	6	1.04	[0.80; 1.36]	6.1%
Huang et al., 2018	Pred + ARBs/ACEi	1.67 (0.11)	0.37 (0.08)	52	12	0.22	[0.21; 0.23]	6.4%
Ramachandran et al., 2014	Tac + Pred + ARBs + atorvastatin	4.57 (3.6)	0.52 (0.5)	23	12	0.11	[0.08; 0.16]	5.8%
Segarra et al., 2002	Pred + Tac + ACEi/ARBs +/– other AH +/– statins	10.3 (9.5)	2.6 (3.2)	25	12	0.25	[0.16; 0.39]	5.6%
Segarra et al., 2007	MMF + ACEi/ARBs +/– other AH +/– statins	7.2 (3.2)	3.02 (2.1)	22	12	0.42	[0.33; 0.54]	6.1%
Mahmoud et al., 2005	CsA + Pred +/– ketoconazole	6.6 (2)	1.89 (0.33)	45	21	0.29	[0.27; 0.31]	6.4%
Mahmoud et al., 2005	CsA + Pred +/– ketoconazole	6.7 (2.2)	0.38 (0.15)	61	22.6	0.06	[0.05; 0.06]	6.4%
Singh et al., 1999	CSA	7.1 (7.13)	1.8 (3.43)	42	22.8	0.25	[0.15; 0.42]	5.4%
Ingulli et al., 1995	CsA + Pred +/– furosemide	6.2 (0.2)	2 (0.1)	21	27.5	0.32	[0.32; 0.33]	6.4%
Risler et al., 1996	Pred + AsA then CsA	5.4 (5.2)	2.5 (1.8)	23	36	0.46	[0.32; 0.66]	5.8%
Risler et al., 1996	Pred +/– chl+/– CsA	3.4 (4.9)	2.3 (1.1)	24	36	0.68	[0.41; 1.13]	5.3%
Heering et al., 2004	Pred + AsA +/– CsA	5.2 (1.1)	3.63 (1.41)	34	48	0.70	[0.62; 0.78]	6.3%
Heering et al., 2004	Pred +/– chl/CsA	4.6 (3.1)	2.04 (0.52)	23	48	0.44	[0.35; 0.56]	6.1%
Segarra et al., 2011	CsA + MMF + ACEi/ARBs +/– diuretics +/– statins	7.74 (3.9)	4.26 (2.02)	27	60	0.55	[0.46; 0.66]	6.2%
Futrakul et al., 2004	ACEi + CCB + AP + vitamins E and C +/– ARB + Pred	3.1 (4.43)	0.2 (1.26)	10	120	0.06	[0.00; 2.27]	0.6%
Random effects model						**0.35**	**[0.27; 0.47]**	**100.0%**
Prediction interval							**[0.10; 1.26]**	

Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.3366$, $p = 0$
Test for overall effect: $z = -7.06$ ($p < 0.01$)

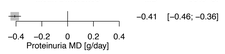


Change in daily proteinuria is expressed as ratio of means (response ratio) between last timepoint reported and baseline measurements. ROM, ratio of means; 95% CI, 95% confidence interval; N, number of patients in sample group; Tac, tacrolimus; CNI, calcineurin inhibitors; CsA, cyclosporine A; MMF, mycophenolate mofetil; CYC, cyclophosphamide; RTX, rituximab; ACEi/ARB, treatment with either ACE alone, ARB alone, or a combination or both; Pred, prednisone; AH, antihypertensives; Asa, acetylsalicylate; chl, chloramphenicol; CCB, calcium channel blockers; AP, antiplatelets. Summary effect of all studies, regardless of the type of immunosuppressive therapy is highlighted in bold.

- In patients treated with immunosuppressants, independently of their class, a reduction in daily proteinuria of more than 50% was observed from baseline to the last follow-up (ROM, 0.35; 95% CI, 0.27 to 0.47) (**Figure 2**)
- A more prominent decrease in daily proteinuria was observed at 12 months (ROM, 0.34; 95% CI, 0.19 to 0.62) when compared to daily proteinuria collected at 6 months (ROM, 0.59; 95% CI, 0.37 to 0.94)

Figure 3. Comparison of immunosuppressive treatment vs non-immunosuppressive treatment on daily proteinuria.

Study	Intervention	Baseline mean (sd)	N Tx	Tx mean (sd)	N Ctrl	Ctrl mean (sd)	Timepoint (mo)	MD	95%–CI
Huang et al., 2018	Pred + ARBs/ACEi	1.63 (0.13)	52	0.37 (0.08)	50	0.78 (0.15)	12	–0.41	[–0.46; –0.36]



Treatment effect is expressed as a mean difference between the intervention and control arms at the last timepoint (prednisone + ACE/ARBs vs ACE/ARBs alone). MD, mean difference; 95% CI, 95% confidence interval; N, number of patients in sample group.

- Only one controlled study (Huang et al., 2018) allowed estimating the effect of immunosuppressive vs non-immunosuppressive therapies (Prednisone + ACEi/ARBs vs ACEi/ARBs), and the result showed that addition of immunosuppressants to the treatment regimen resulted in a stronger reduction in daily proteinuria than when treating only with ACEi/ARBs (MD -0.41; 95% CI: -0.46; -0.36) (**Figure 3**). However, it must be noted that, in contrast to most primary FSGS studies which look at nephrotic patients, this study was conducted in patients with subnephrotic proteinuria (1-3.5 g/24h).

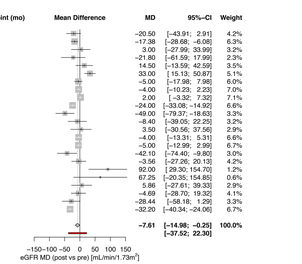
Effect on renal function

- 20 studies were considered eligible to estimate the mean difference in glomerular filtration rate between various follow-up and baseline measurements. Glomerular filtration rate was reported as either eGFR (n=18 studies) or as creatinine clearance (CrCl, n= 2 studies).

Figure 4. Change in eGFR in patients treated with immunosuppressants.

Study	Intervention	Baseline mean (sd)	Timepoint mean (sd)	N	Timepoint (mo)	MD	95%–CI	Weight
Lieberman et al., 1996	CsA +/– CCB	103.4 (36.7)	82.9 (19.1)	12	6	–20.50	[–43.91; 2.91]	4.2%
Ramachandran et al., 2014	Tac + Pred + ARBs + atorvastatin	101.6 (24.4)	84.22 (29.43)	44	6	–17.38	[–28.68; –6.08]	6.3%
Choi et al., 2002	MMF +/– steroids or CsA or AZA + ACEi/ARBs	66.5 (43.8)	69.5 (50.8)	18	6	3.00	[–27.99; 33.99]	3.2%
Bhimma et al., 2006	Pred + Tac + ACEi + diuretics + CCB	117.4 (74)	95.6 (52.6)	20	12	–21.80	[–61.59; 17.99]	2.3%
Dimkovic et al., 2009	Steroids + MMF + ACEi +/– ARBs or statins	56.2 (33.2)	70.7 (39.6)	13	12	14.50	[–13.59; 42.59]	3.5%
Gellermann et al., 2012	MP + Pred + CsA +/– ACEi and/or ARBs +/– diuretics then MMF	106.19 (26.27)	139.19 (25.29)	16	12	33.00	[15.13; 50.87]	5.1%
Segarra et al., 2002	Pred + Tac + ACEi/ARBs +/– other AH +/– statins	73 (16)	68 (28)	25	12	–5.00	[–17.98; 7.98]	6.0%
Segarra et al., 2007	MMF + ACEi/ARBs +/– other AH +/– statins	67.1 (6.3)	63.1 (13.5)	22	12	–4.00	[–10.23; 2.23]	7.0%
Gulati et al., 2000	Pred or Pred + CYC	92 (11)	94 (12)	36	14.6	2.00	[–3.32; 7.32]	7.1%
Gulati et al., 2000	Pred or Pred + CYC	94 (14)	70 (24)	36	17.8	–24.00	[–33.08; –14.92]	6.6%
El–Refaey et al., 2007	Pred +/– CsA +/– MMF + ACEi	136.6 (65)	87.6 (50)	28	18	–49.00	[–79.37; –18.63]	3.3%
Hogg et al., 2013	CsA + Pred + ACEi or ARB +/– additional AH	126.8 (50.5)	118.4 (53.2)	22	18	–8.40	[–39.05; 22.25]	3.2%
Hogg et al., 2013	MMF/DEX + Pred + ACEi or ARB +/– additional AH	122.6 (50.7)	126.1 (58.9)	20	18	3.50	[–30.56; 37.56]	2.9%
Senthil Nayagam et al., 2008	MMF + Pred + ACEi/ARBs +/– other AH +/– diuretics +/– statins	87 (14.2)	83 (13.5)	17	20	–4.00	[–13.31; 5.31]	6.6%
Senthil Nayagam et al., 2008	Pred + ACEi/ARBs +/– other AH +/– diuretics +/– statins	84 (10.1)	79 (12.8)	16	20	–5.00	[–12.99; 2.99]	6.7%
El–Refaey et al., 2007	Pred +/– CsA +/– MMF + ACEi	96.1 (49.1)	54 (24)	11	31	–42.10	[–74.40; –9.80]	3.0%
Choi et al., 2001	Pred + CsA +/– ACEi	118.31 (29.43)	114.75 (38.37)	16	32	–3.56	[–27.26; 20.13]	4.2%
Adikhari et al., 1997	CYC + MP + Pred	63.14 (50.89)	155.14 (67.63)	7	38	92.00	[29.30; 154.70]	1.2%
Adikhari et al., 1997	Shorter CYC + MP + Pred	97.25 (78.86)	164.5 (45.5)	4	38	67.25	[–20.35; 154.85]	0.6%
Mendoza et al., 1990	Pred + MP +/– CYC or chl	133.36 (63.29)	139.22 (49.09)	22	46	5.86	[–27.61; 39.33]	2.9%
Agrawal et al., 2019	Tac + steroids	102.81 (25.85)	98.13 (19.56)	7	60	–4.69	[–28.70; 19.32]	4.1%
Agrawal et al., 2019	Tac + steroids	91.56 (24.41)	63.11 (31.86)	7	60	–28.44	[–58.18; 1.29]	3.3%
Segarra et al., 2011	CsA + MMF + ACEi/ARBs +/– diuretics +/– statins	88.6 (16.5)	56.4 (13.9)	27	60	–32.20	[–40.34; –24.06]	6.7%
Random effects model						**–7.61**	**[–14.98; –0.25]**	**100.0%**
Prediction interval							**[–37.52; 22.30]**	

Heterogeneity: $I^2 = 81\%$, $\tau^2 = 192.7093$, $p < 0.01$
Test for overall effect: $z = -2.03$ ($p = 0.04$)



Change in eGFR are expressed as mean difference between last timepoint and baseline measurements. MD, mean difference, 95% CI, 95% confidence interval; N, number of patients in sample group; Tac, tacrolimus; CNI, calcineurin inhibitors; CsA, cyclosporine A; MMF, mycophenolate mofetil; CYC, cyclophosphamide; RTX, rituximab; ACEi/ARB, treatment with either ACE alone, ARB alone, or a combination or both; Pred, prednisone; MP, methylprednisolone; AH, antihypertensives; Asa, acetylsalicylate; chl, chloramphenicol; CCB, calcium channel blockers; AP, antiplatelets. Summary effect of all studies, regardless of the type of immunosuppressive therapy is highlighted in bold.

- In studies reporting eGFR, mean GFR 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; -0.25) (**Figure 4**)
- A statistically significant reduction of eGFR was observed after various months of follow-up (eg, 6, 18, 31, 38, and 60 months). However, there was no clear correlation between the length of follow-up and the observed effect size (data not shown).
- A statistically significant reduction in CrCl of 25.0 ml/min/1.73 m^2 (MD -25.03; 95% CI: -59.33; -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 (data not shown)

Safety and tolerability results

- 46 out of the 98 included studies showed safety and tolerability outcomes potentially related to the use of immunosuppressants, either as a monotherapy or in combination with other drug classes. However, lack of controlled studies precludes the possibility to reliably conclude on the safety and tolerability profile of these therapies.
- Hypertension and infections were more frequently observed in patient cohorts treated with CNI (such as CsA) than with other classes of immunosuppressants, although these were also the main adverse events caused by steroids and cyclophosphamide (CYC)
- One study reported steroid-related death due to sepsis in 2 patients (Arias et al., 2011) and another study assessing the effect of CsA monotherapy documented the death of 1 patient (Gorsane et al., 2016). Other mortality events were not associated with treatment.
- Other side effects, such as hospitalization or edema, were not common among the different treatment cohorts, and could not be associated to a specific immunosuppressive therapy

Conclusions

- This systematic literature review supports that patients treated with immunosuppressants demonstrate, on average, a decrease in proteinuria from baseline to varying follow-up timepoints when using prednisone plus ACEi/ARBs compared to ACEi/ARBs
- CrCl and eGFR changes from baseline to follow-up show different extents of effect between both outcomes
- The effect of immunosuppressive treatment on renal survival is uncertain due to the high degree of variability among the available studies
- Due to the apparent heterogeneity observed among studies and the lack of properly controlled studies, it is hard to attribute how much of the observed effect is due to immunosuppressive treatment, stressing the low certainty evidence currently available in the literature and the need for better designed studies to reliably assess the effect of immunosuppressants on primary FSGS patients

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