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META-ANALYSIS

Rituximab or plasmapheresis for prevention of recurrent focal segmental glomerulosclerosis after kidney transplantation: A systematic review and meta-analysis

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Abstract

BACKGROUND

Focal segmental glomerulosclerosis (FSGS) is one of the most common glomerular

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diseases leading to renal failure. FSGS has a high risk of recurrence after kidney transplantation. Prevention of recurrent FSGS using rituximab and/or plasmapheresis has been evaluated in multiple small studies with conflicting results.

AIM

To assess the risk of recurrence of FSGS after transplantation using prophylactic rituximab with or without plasmapheresis, and plasmapheresis alone compared to the standard treatment group without preventive therapy.

METHODS

This meta-analysis and systematic review were performed by first conducting a literature search of the MEDLINE, EMBASE, and Cochrane databases, from inception through March 2021; search terms included 'FSGS,' 'steroid-resistant nephrotic syndrome', 'rituximab,' and 'plasmapheresis,'. We identified studies that assessed the risk of post-transplant FSGS after use of rituximab with or without plasmapheresis, or plasmapheresis alone. Inclusion criteria were: Original, published, randomized controlled trials or cohort studies (either prospective or retrospective), case–control, or cross-sectional studies; inclusion of odds ratio, relative risk, and standardized incidence ratio with 95% confidence intervals (CI), or sufficient raw data to calculate these ratios; and subjects without interventions (controls) being used as comparators in cohort and cross-sectional studies. Effect estimates from individual studies were extracted and combined using a random effects model.

RESULTS

Eleven studies, with a total of 399 kidney transplant recipients with FSGS, evaluated the use of rituximab with or without plasmapheresis; thirteen studies, with a total of 571 kidney transplant recipients with FSGS, evaluated plasmapheresis alone. Post-transplant FSGS recurred relatively early. There was no significant difference in recurrence between the group that received rituximab (with or without plasmapheresis) and the standard treatment group, with a pooled risk ratio of 0.82 (95%CI: 0.47-1.45, I^2 = 65%). Similarly, plasmapheresis alone was not associated with any significant difference in FSGS recurrence when compared with no plasmapheresis; the pooled risk ratio was 0.85 (95%CI: 0.60-1.21, I^2 = 23%). Subgroup analyses in the pediatric and adult groups did not yield a significant difference in recurrence risk. We also reviewed and analyzed post-transplant outcomes including timing of recurrence and graft survival.

CONCLUSION

Overall, the use of rituximab with or without plasmapheresis, or plasmapheresis alone, is not associated with a lower risk of FSGS recurrence after kidney transplantation. Future studies are required to assess the effectiveness of rituximab with or without plasmapheresis among specific patient subgroups with high-risk for FSGS recurrence.

Key Words: Focal segmental glomerulosclerosis; Kidney transplantation; Meta-analysis; Plasmapheresis; Transplantation; Systematic review

Core Tip: Focal segmental glomerulosclerosis (FSGS) is associated with a high risk of recurrence after kidney transplantation. Plasmapheresis and/or rituximab has been used to prevent recurrence with conflicting results. This meta-analysis is among the first to report that the use of preemptive rituximab, either alone or in combination with plasmapheresis, or plasmapheresis alone, did not alter the recurrence risk of FSGS after kidney transplantation.

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is an important glomerular cause of end-stage kidney disease, and is associated with a high risk of disease recurrence after kidney transplantation[1-5]. Approximately 30% of patients[6,7] develop recurrent FSGS following kidney transplantation, with studies reporting a range between 17% and 55%[8]. FSGS has been shown to negatively affect overall graft survival[9-12]. Although the exact pathogenesis of this disease is unknown, it is believed that circulating factors affecting podocytes and glomerular permeability may play an important role. FSGS recurrence presents early after kidney transplantation; thus, supporting the pathophysiological role of circulating factors.

Treatment for recurrent FSGS in kidney transplant recipients is difficult. Steroids have been used as the main therapy in adults. Unfortunately, only 50% of patients achieve remission following a course of steroid treatment[13]. Furthermore, a large proportion of patients relapse, eventually becoming either steroid-resistant, or steroid-dependent[14]. Plasmapheresis has been effectively used to treat recurrent FSGS after kidney transplantation, purportedly by removing pathophysiological circulating factors and inducing FSGS remission. Preemptive plasmapheresis following kidney transplantation has been proposed as a preventive measure for FSGS.

Rituximab is a monoclonal, chimeric antibody against CD20+ B lymphocytes, and has been used to both prevent and treat recurrent FSGS after kidney transplantation. In 2020, Hansrivijit and Ghahramani[15] reported promising outcomes after treatment of recurrent FSGS in kidney transplant recipients, using either a combination of rituximab and plasmapheresis, or plasma exchange alone. Their study demonstrated an overall remission rate of 72.7%, determined by a significant reduction in serum creatinine levels and the degree of proteinuria. Nevertheless, the efficacy of rituximab or plasmapheresis as a preventive measure for post-transplant recurrent FSGS remains controversial.

This systematic review and meta-analysis were conducted to explore the effectiveness of rituximab–with or without plasmapheresis–compared with plasmapheresis alone, for the prevention of recurrent FSGS after kidney transplantation.

MATERIALS AND METHODS

Search strategy

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines[16]. A literature search was performed to identify studies that investigated the effect of preventive use of plasmapheresis and/or rituximab on the risk of recurrent FSGS after kidney transplantation. This was independently conducted by two investigators (Boonpheng B and Hansrivijit P) in the MEDLINE, EMBASE, and Cochrane databases, from inception through March 2021. Search terms included 'FSGS', 'steroid-resistant nephrotic syndrome', 'rituximab', and 'plasmapheresis'. The references of selected articles were manually searched for additional relevant studies. There were no language restrictions.

Inclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) Original, published, randomized controlled cohort (either prospective or retrospective), case-control, or cross-sectional studies; (2) The odds ratio, relative risk, and standardized incidence ratio with 95% confidence intervals (CIs), or sufficient raw data to calculate these ratios, were provided; and (3) Subjects without interventions (controls) were used as comparators in cohort and cross-sectional studies.

Study eligibility was independently assessed by the investigators. Any disagreements were resolved through mutual consensus. The quality of each study was assessed utilizing the Newcastle-Ottawa Quality Scale[17]. This scale assesses each study using three categories: (1) The representativeness of the subjects; (2) The comparability between the study groups; and (3) Ascertainment of the exposure or

outcome of interest for case-control and cohort studies respectively.

Review process and data extraction

Two investigators independently reviewed the titles and abstracts of all retrieved articles. Articles that did not fulfill the inclusion criteria were excluded. Only potentially relevant articles underwent full-text reviews to determine eligibility. A standardized data collection form was used to extract the following data: First author's name, year of publication, year of study, country of origin, study design, source of population, number of subjects, baseline characteristics of the subjects, and effect estimates. This data extraction process was performed in duplicate to ensure accuracy.

Statistical analysis

All statistical analyses were performed using R version 3.2.0 (the R Foundation for Statistical Computing, Vienna, Austria). The pooled risk ratios for recurrent FSGS in the active intervention group compared with the no intervention group were calculated using the generic inverse method of DerSimonian and Laird[18]. A random effects model was utilized given the high likelihood of between-study variance due to differences in underlying population as well as methodology. Cochran's Q-test, supplemented by the I^2 statistic, was used to evaluate statistical heterogeneity. This statistic quantifies the proportion of total variation across studies due to true heterogeneity rather than chance. An I^2 value of 0-25% represented insignificant heterogeneity, 25%-50% represented low heterogeneity, 50%-75% represented moderate heterogeneity, and > 75% represented high heterogeneity[19].

RESULTS

The initial search yielded 813 articles, all of which underwent both title and abstract reviews. Most were excluded at this step as they did not fulfill our inclusion criteria; *i.e.*, they were case reports, letters to the editor, review articles, or interventional studies. A total of 38 studies underwent full-length article review. Of 17 were excluded, as they did not include controls or report the outcome of interest. A total of 21 observational studies, including 920 patients, met our inclusion criteria[8,20-39] and were included in the meta-analysis. Figure 1 outlines our search methodology and selection process. The baseline characteristics of the included studies are summarized in Tables 1-4 (detailed characteristics in Tables 3 and 4).

Preemptive rituximab

Eleven studies[22-31,39], with a total of 399 kidney transplant recipients with FSGS, evaluated the use of rituximab with or without plasmapheresis. There was no significant difference in recurrence between the group that received rituximab (with or without plasmapheresis) and the standard treatment group, with a pooled risk ratio of 0.82 (95%CI: 0.47-1.45, I^2 = 65%). Figure 2 shows the forest plot.

Subgroup analysis, based on five studies[22-24,30,31] that evaluated preemptive rituximab use without concurrent plasmapheresis compared with no intervention, also showed no significant association; the pooled risk ratio was 0.82 (95%CI: 0.23-2.92, I^2 = 81%).

Four studies[24,29-31] selected only patients deemed to be at high-risk of recurrence, based on demographic and clinical criteria. Only the study by Fornoni *et al*[24] showed a significantly lower recurrence risk in the rituximab group. The remaining three studies reported a numerically higher recurrence in the rituximab group[29-31].

Sensitivity analyses were also performed after excluding five studies[22,23,25,27,28,39] that did not report the rituximab dose or protocol; all were published as abstracts. The risk ratio was also not significant (risk ratio: 1.09, 95%CI: 0.37-3.19).

Preemptive plasmapheresis

Thirteen studies[8,20,21,25-27,32-38], including 571 kidney transplant recipients with FSGS, evaluated the use of plasmapheresis alone. Compared with no plasmapheresis, plasmapheresis was not found to be associated with any significant difference in FSGS recurrence, with a pooled risk ratio of 0.85 (95%CI: 0.60-1.21, I^2 = 23%, Figure 3). Subgroup analysis in pediatric patients also did not yield a significant association, with a pooled risk ratio of 0.86 (95%CI: 0.29-4.49, I^2 = 63%).

Sensitivity analysis, after excluding three studies[25,27,34] that were published as abstracts and did not report the protocol or regimen of plasmapheresis, did not show a significant change in the risk ratio (1.07, 95%CI: 0.66-1.72, I^2 =22%).

Table 1 Characteristics of included studies evaluating the outcomes of preemptive plasmapheresis

Ref.	Country	Design	*n* (%)	Population	Age	PP protocol	Def of recurrence	Recurrence	Graft survival	Quality assessment
Kawaguchi *et al*[20], 1994	Japan	Retrospective	14	FSGS children	2-12 yr at FSGS Dx	2-3 sessions immediately before KT (-5, -3, and -1 d) ATG 7-14 d pre-op	N/A	3/8 (38%) *vs* 4/6 (67%)	93% graft survival in overall cohort	Fair, 4-1-2
Otsubo *et al*[21], 1999	Japan	Retrospective	37	FSGS undergoing KT	22 yr at KT	N/A	Clinical and biopsy in all cases	4/19 (21%) *vs* 9/18 (50%)	75%at 5 yr, 63% at 10 yr	Fair, 4-1-2
Iguchi *et al*[32], 1997	Japan	Prospective cohort	11	FSGS undergoing KT	33.3 (20-43) yr	3 sessions of pre-op PP within 3 d before KT	Clinical and/or pathologic	1/3 (33%) *vs* 4/8 (50%)	100% *vs* 63.6%	Fair, 4-2-2
Ohta *et al*[33], 2001	Japan	Retrospective	21	FSGS children	Age of FSGS onset 69.5 ± 36.4 mo (range 9-134 mo)	1-2 sessions immediately before KT (-5, -3, and -1 d). Therapeutic PP until reduction of proteinuria	Clinical and/or pathologic	5/15 (33%) *vs* 4/6 (67%)	13/15 *vs* 3/5 (1 death with functioning graft in Non-PP)	Fair, 4-2-2
Somers and Baum[34], 2009	United States	Retrospective	52	FSGS children	12.5 yr	N/A	N/A	5/19 (26%) *vs* 18/33 (55%)	Overall, 11/52 graft loss	Fair, 4-1-2
Gonzalez *et al*[35], 2011	United States	Retrospective	34	FSGS children	Age at KT: 13 ± 5 yr. Age at FSGS diagnosis: 5.3 yr (n = 19, recurrence group), 6.9 yr (n = 15, no recurrence group)	1-10 sessions	Clinical and/or pathologic	9/17 (53%) *vs* 10/17 (59%)	Graft loss at 3 yr: 25% in recurrence group *vs* 20% in non-recurrence	High, 4-2-3
Miyauchi *et al*[25], 2011	Japan	Prospective cohort	25	FSGS undergoing KT	N/A	N/A	N/A	3/9 (33%) *vs* 2/4 (50%)	N/A	Low, 3-1-1
Park *et al*[26], 2014	South Korea	Retrospective	27	FSGS undergoing KT	Age at KT: 39 ± 14 yr and 36 ± 11 yr	PP and IVGV infusion after each session of PP prior to transplantation	Clinical confirmed by biopsy	1/4 (25%) *vs* 5/18 (27%)	FSGS with recurrence had less graft survival than those without recurrence (P = 0.01)	High, 4-2-3
Okumi *et al*[27], 2015	Japan	Retrospective	38	FSGS undergoing KT	N/A	N/A	N/A	4/10 (40%) *vs* 2/5 (40%)	5/38 graft loss overall	Low, 3-1-1
Verghese *et al*[36], 2018	United States	Retrospective	57	FSGS children	Age at KT: 13.2 ± 4.5 yr (after 2006 with PP) *vs* 10.4 ± 5.4 yr (before 2006, no PP)	LDKT: 3 sessions PP pre-op. DDKT: 1 session of PP pre-op. Post-op: 5 sessions of PP every other day starting POD1	Biopsy; if unable to do biopsy, persistent nephrotic range proteinuria	7/26 (27%) *vs* 8/31 (26%)	Death-censored graft survival not sig different (P = 0.61)	High, 4-2-3
Koyun *et al*[37], 2019	Turkey	Retrospective	46	FSGS children	Age at KT: 7.2 ± 1.2 yr (PP) *vs* 10.7 ± 4.5 yr (no PP)	LDKT: 2-5 sessions of PP pre-op. DDKT: 1 session of PP pre-op. Post-op: 5 session of early PP	N/A	3/6 (50%) *vs* 5/40 (12.5%)	N/A	Low, 3-1-1
Campise *et al*[38], 2019	Italy	Retrospective	73	FSGS undergoing	Age at FSGS Dx: 27 (15-35) yr. Age at KT: 41 (38-52) yr	2003-2008: post-transplant PP only 2008-2014: 1 session immediately before	Post-transplant proteinuria; confirmed	Biopsy-proven: 5/21 (24%) *vs*	Death-censored graft survival: 81% (17/21) *vs*	High, 4-2-3

				KT		surgery and 3 sessions *per* week for 3 consecutive weeks from POD1	by biopsy	12/52 (23%)	84% (44/52) (P = 0.7022)	
Uffing *et al* [8], 2020	United States, Europe, Brazil	Retrospective, multicenter	176	FSFS adults undergoing KT	Age at KT: 38 (29–47) yr. Age at FSGS Dx: 27 (17-40) yr	N/A	N/A	9/22 (41%) *vs* 48/154 (31%)	Graft failure 15% w/o recurrence and 39% with recurrence	High, 4-2-3

N: Number; ESKD: End-stage kidney disease; FSGS: Focal segmental glomerulosclerosis; PP: Plasmapheresis; KT: Kidney transplantation; RTX: Rituximab; N/A: Not available.

Timing of recurrence

Although only five studies reported the timing of post-transplant recurrent FSGS, it appears that most cases occurred relatively early. Park *et al*[26] reported the time to recurrence in all 6 patients with recurrent FSGS: 3 patients experienced early recurrence, within the first week; 1 experienced a recurrence within the first month; and 3 experienced late recurrence, at 6–12 mo. Verghese *et al*[36] included a Kaplan-Meier curve for FSGS recurrence; this was not significantly different between the two intervention groups, but again showed a trend towards early recurrence. In the study by Alasfar *et al*[29], the median time to recurrence of the entire cohort was 1.25 mo (range: 1 d to 30 mo). Similarly, Auñón *et al*[31] and Uffing *et al*[8] reported the median time to recurrence as 3 and 1.5 mo, respectively. Overall, this data supports the hypothesis that pre-existing circulating factors play a role in FSGS recurrence.

Effects on allograft function

Some studies reported decreased allograft survival in patients who experienced FSGS recurrence compared to those who did not[8,26,31-33,35,39]. Allograft survival appears to depend on response to recurrent FSGS therapy, which variably consists of plasmapheresis with more intensive immunosuppressive regimens. Neither pre-emptive plasmapheresis or rituximab *per se* seems to have effects on allograft survival.

Evaluation for publication bias

The funnel plots for the outcomes of rituximab and plasmapheresis are shown in Figures 4 and 5, respectively. They are symmetrical, and do not suggest the presence of publication bias in favor of positive studies. Egger's asymmetry test yielded P-values of 0.56 and 0.83 for the rituximab and the plasmapheresis groups, respectively.

DISCUSSION

Primary FSGS often recurs after kidney transplantation, leading to graft loss and morbidity[6-8]. Multiple basic science and clinical studies have implicated circulating factors in the pathogenesis of recurrent FSGS[40-42]. The tendency of recurrent FSGS

Table 2 Characteristics of included studies evaluating the outcomes of preemptive rituximab

Ref.	Country	Design	*n* (%)	Population	Age	Rituximab dose and protocol	Concurrent PP	Def of recurrence	Recurrence	Graft survival	Follow-up duration	Quality assessment
Burke *et al* [22], 2009	United States	Retrospective	29	FSGS undergoing KT	Age at KT: 6-21 yr	N/A	No	New onset proteinuria	6/18 (33%) *vs* 8/11 (72%)	No significant difference in graft survival	N/A	Fair, 3-1-2
Sagheshima *et al*[23], 2010	United States	Prospective	40	FSGS undergoing KT	Age at KT: 4-24 yr	N/A	No	UPCR > 3.5 post-transplant	8/29 (28%) *vs* 7/11 (64%)	N/A	N/A	Low, 3-1-1
Fornoni *et al* [24], 2011	United States	Retrospective	41	High-risk pediatric/young adult FSGS undergoing KT: (< 25 yr at FSGS Dx or progression to ESKD within 7 yr)	Age at KT: 15 ± 5.5 yr (rituximab), 12.3 ± 5.2 yr (control)	One dose of rituximab (375 mg/m^2) within 24 h of kidney transplantation	No	UPCR > 3.5 within 30 d post-transplant or need for PP. Protocol biopsy in 20/27 (74%)	7/27 (26%) *vs* 9/14 (64%)	1-yr graft survival: 95.8% *vs* 85.7% (P = 0.26)	N/A	High, 4-1-3
Miyauchi *et al*[25], 2011	Japan	Prospective	25	FSGS undergoing KT	N/A	N/A	N/A	N/A	2/12 (17%) *vs* 5/13 (38%)	N/A	N/A	Low, 3-1-1
Park *et al* [26], 2014	South Korea	Retrospective	27	FSGS undergoing KT	Age at KT: 39 ± 14 yr (n = 7, recurrence), 36 ± 11 yr (n = 20, no recurrence)	PP and IVGV infusion after each session of PP prior to transplantation, and RTX (375 mg/m^2) was administeredwithin 1 wk prior to transplantation	Yes	Clinical confirmed by biopsy	1/4 (25%) *vs* 5/18 (27%)	FSGS with recurrence had less graft survival than those without recurrence (P = 0.01)	N/A	High, 4-1-3
Okumi *et al* [27], 2015	Japan	Retrospective	38	FSGS undergoing KT	N/A	N/A	Yes	N/A	5/23 (22%) *vs* 6/15 (40%)	5/38 graft loss overall. Cr at yr 2 and 6 significantly lower in those who received both R + PP	N/A	Low, 3-1-1
Futamura *et al*[28], 2016	Japan	Retrospective	28	FSGS undergoing KT	N/A	N/A	Yes	N/A	3/7 (43%) *vs* 5/21 (24%)	N/A	N/A	Low, 3-1-1
Alasfar *et al* [29], 2018	United States	Prospective	64	High-risk FSGS undergoing KT (2 of: white, age ≤ 30 at Dx, progression to ESKD ≤ 5 yr. Albumin < 3 g/dL during disease course, h/o failed KT due to recurrence)	Age at FSGS Dx: 29.9 ± 17.2. Age at KT: 38 ± 16.5	Rituximab was given in 1 or 2 doses (375 mg/m^2*per* dose)	Yes; 3-10 sessions of PP day-7 to POD 2	Clinical and biopsy	23/37 (62%) *vs* 14/27 (51%)	Trend toward better renal allograft survival in nonrecurrent group comparedto the recurrent group (P = 0.0662)	29.5 mo	High, 4-1-3
Lu *et al*[30], 2018	United States	Retrospective	55	High-risk FSGS undergoing KT considered (age ≤ 25 at Dx, proteinuria ≥ 5 g/d, progression to ESKD ≤ 5-7 yr)	Age at KT: 44	One dose of rituximab (375 mg/m^2, max 100 mg)	No	Proteinuria and biopsy	4/7 (57%) *vs* 6/48 (13%)	Graft loss: 1/7 (14%) *vs* 8/48 (17%)	N/A	Fair, 3-2-2

Auñón *et al* [31], 2021	Spain	Retrospective, multicenter	34 (93 total cohort)	High-risk FSGS undergoing KT considered (hypoalbuminemia and NS at baseline); genetic form excluded	Age at KT: 35.0 ± 15.2 (R group), 42.4 ± 12.2 (non-R group)	Rituximab, 1 g at induction and 1 g on day 14 after transplantation	No	Recurrence of proteinuria, confirmed by biopsy	6/12 (50%) *vs* 9/22 (41%)	53.5% with recurrence *vs* 88.5% in non-recurrence group	N/A	High, 4-1-3
Mukku *et al* [39], 2021	United States	Retrospective	18	FSGS undergoing KT	Age at KT: 35 yr	N/A	Yes	Recurrence of proteinuria	0/8 *vs* 3/10 (30%)	8/8 *vs* 9/10	30 (1-36) mo	Low, 3-1-1

N: Number; ESKD: End-stage kidney disease; FSGS: Focal segmental glomerulosclerosis; PP: Plasmapheresis; KT: Kidney transplantation; RTX: Rituximab; N/A: Not available.

to present early and rapidly after kidney transplantation supports the pathophysiologic role of circulating factors[43]. Case reports of successful kidney allograft transfers from recipients with severe, early, refractory recurrent FSGS, to recipients without a history of primary FSGS, also indirectly suggest the role of circulating factors in disease recurrence[44,45].

Plasmapheresis is considered an effective treatment able to induce remission in established recurrent diseases[46]. Likewise, plasmapheresis has been used as a prevention of FSGS after kidney transplant. By rapidly removing pre-existing circulating factors, especially in conjunction with immunosuppressive medication, it is presumed that some of the putative circulating factors can be eliminated or suppressed to the level low enough not to affect glomerular permeability. Plasmapheresis is performed prior to kidney transplantation in an attempt to prevent FSGS recurrence and associated allograft injury, which may affect graft survival[9,10].

More recently, rituximab has been effectively used to treat many glomerular diseases, including FSGS[47]. The exact mechanism of rituximab in the treatment of FSGS is unknown; however, it is believed that rituximab may have a B-cell-independent effect on podocyte cytoskeletal stabilization, in addition to its B-cell depleting effects[48]. Therefore, rituximab is also utilized to prevent FSGS recurrence, either alone or in combination with plasmapheresis.

Our meta-analysis is among the first to report that the use of preemptive rituximab (either alone or in combination with plasmapheresis) or plasmapheresis alone did not alter the recurrence risk of FSGS after kidney transplantation. To increase power, we combined the patients who received rituximab alone and those who received both rituximab and plasmapheresis into the same group. This might have overestimated the effect of rituximab. However, sensitivity analyses in the subgroup that received rituximab alone or rituximab with plasmapheresis did not change the association so this is unlikely to be significant. The timing of recurrence was also not affected by the preventive measure. In contrast, rituximab and plasmapheresis have been shown to be effective for the treatment of recurrent FSGS after kidney transplantation. The efficacy and safety of combined rituximab and plasmapheresis in patients with recurrent FSGS was recently demonstrated in a meta-analysis, reporting that up to 72.7% of patients achieved remission[15]; of these, most patients achieved complete remission. The

Table 3 Detailed characteristics of included studies evaluating the outcomes of preemptive plasmapheresis

Ref.	Country	Age	Genetic testing	Race	Time to ESKD	Repeat KT	Induction	IS	Donor types	Biopsy	Follow-up duration
Kawaguchi *et al*[20], 1994	Japan	2-12 yr at FSGS Dx	N/A	Asian	12–117 mo		ATG only in PP group	CS, CsA, AZA/mizolibine	13/14 living1/14 DDKT	N/A	N/A
Otsubo *et al* [21], 1999	Japan	22 yr at KT	N/A	Asian	N/A	N/A	CS, CsA/Tac	CS, CsA/Tac, AZA/mizolibine	34/37 LRKT, 4/37 DDKT	Per-cause biopsy	N/A
Iguchi *et al* [32], 1997	Japan	33.3 (20-43) yr	N/A	Asian	N/A	None	ATG during first 2 wk in PP group	CS, CsA, AZA	100% LRKT	Intra-op biopsy (1 h) in all cases then as clinically indicated	N/A
Ohta *et al* [33], 2001	Japan	Age of FSGS onset69.5 ± 36.4 mo (range 9-134 mo)	N/A	Asian	51.8 ± 29.6 mo (range 7-120)	1/21	None	CS, CsA/Tac, AZA/mizolibine	3/21 DDKT (14%) *vs* 18/21 (LRKT)	Intra-op biopsy (1 h) in all cases then as clinically indicated	62.7 (PP group), 41.6 mo (non-PP group)
Somers and Baum[34], 2009	Unite States	12.5 yr (85% white)	N/A	85% White	3 yr (median)	N/A	N/A	CsA-based regimen	42% living donor	N/A	N/A
Gonzalez *et al*[35], 2011	United States	Age at KT: 13 ± 5 yr	NPHS2 mutation testing on 10 patients (9 tested negative, 1 with heterozygous mutation)	29% White, 15% African, 44% Hispanic, 12% others	4.2 yr (n = 19, recurrence group), 3.1 yr (n = 15, no recurrence group)	Recurrence in previous graft 5/34	rATG (if ATN) or daclizumab	CS, CsA/Tac, MMF	15/34 living, 19/34 DDKT	Per-cause biopsy	N/A
Miyauchi *et al*[25], 2011	Japan	N/A	N/A	Asian	N/A	N/A	N/A	CS, CsA/Tac, AZA/mizolibine	N/A	N/A	N/A
Park *et al* [26], 2014	South Korea	Age at KT: 39 ± 14 yr (n = 7, recurrence), 36 ± 11 yr (n = 20, no recurrence)	N/A	Asian	46 ± 44 mo (n = 7, recur group), 68 ± 67 mo (n = 20, no recur group)	none	Basiliximab (20 mg) on days 0 and 4	CS, CsA/Tac, MMF	4/27 DDKT, 24/27 living (17/27 LRKT)	Per-cause biopsy	N/A
Okumi *et al* [27], 2015	Japan	N/A	N/A	Asian	N/A	N/A	Basiliximab (after 2002)	CS, CsA/Tac, MMF	N/A	N/A	N/A
Verghese *et al*[36], 2018	United States	Age at KT: 13.2 ± 4.5 yr (after 2006 with PP) *vs* 10.4 ± 5.4 yr (before 2006, no PP)	NPHS2 mutation testing (for those with NPHS2 homozygous mutation, PP not indicated)	N/A	N/A	N/A	93% received lymphocyte depleting induction	Before 2006: AZA (90%), MMF (16%), CsA (97%), CS (97%). After 2006: AZA (12%), MMF (88%), CsA (62%)/Tac (38%), CS (12%)	DDKT 37% *vs* Living 63%	Per-cause biopsy	N/A
Koyun *et al*	Turkey	Age at KT: 7.2 ± 1.2	Genetic testing	N/A	N/A	N/A	N/A	N/A	DDKT 20%,	N/A	N/A

[37], 2019		yr (PP) *vs* 10.7 ± 4.5 yr (no PP)	(unspecified gene panel): 2/6 + in PP group *vs* 14/40+ in control group						Living 80%		
Campise *et al* [38], 2019	Italy	Age at FSGS Dx: 27 (15-35) yr. Age at KT: 41 (38-52) yr	Not done	100% White	5 (1-10) yr, 33% rapid (< 3 yr) progression to ESKD	(7/21) 33% in PP group; previous graft loss due to recurrence	Basiliximab (20 mg) on days 0 and 4	CS, Tac, MMF	100% DDKT	Per-cause biopsy	45 (30-107) mo
Uffing *et al* [8], 2020	Unites States, Europe, Brazil	Age at KT: 38 (29–47) yr. Age at FSGS Dx: 27 (17-40) yr	Not done in most patients	56% White, 11% Black, 5% Hispanic, 5% Asian, 10% mixed, Other or unknown 14%	38 (14–75) mo	25%; prior graft loss due to FSGS 9%	rATG (42%), basiliximab (42%), daclizumab (3%), none (13%)	CS + Tac + MMF (72%), CS + CsA + MMF (17%), Tac + MMF (5%), other 6%	67% DDKT, 22% LRKT, 15% LUKT	Per-cause biopsy	N/A

N: Number; ESKD: End-stage kidney disease; FSGS: Focal segmental glomerulosclerosis; PP: Plasmapheresis; KT: Kidney transplantation; RTX: Rituximab; N/A: Not available; LUKT: Living-related kidney transplantation; CS: Corticosteroids; CsA: Cyclosporine; Tac: Tacrolimus; MMF: Mycophenolate mofetil; AZA: Azathioprine; rATG: Rabbit anti-thymocyte globulin; DDKT: Deceased donor kidney transplantation; LRKT: Living-related kidney transplantation.

authors also described a significant reduction in serum creatinine levels (-0.65 mg/dL) and proteinuria (-4.79 g/d) following treatment[15].

Many studies suggest that recurrent FSGS in kidney transplant recipients is at least partially mediated by circulating factors and/or antibodies[43]. The ineffectiveness of prophylactic rituximab in the prevention of FSGS *via* suppression of antibody production, or plasmapheresis in the removal of pre-formed circulating factors, suggests either circulating factors may be inactive in quiescent FSGS or that removing the putative circulating factors may not be enough to prevent the immunologic cascades that trigger the onset of disease recurrence. It is possible that yet-to-be-identified B-cell-independent immunologic factors may trigger the onset of FSGS recurrence, which leads to production of circulating factors and stimulation of B cells, which are targeted by plasmapheresis and rituximab. The fact that patients who developed FSGS recurrence despite pre-emptive plasmapheresis or rituximab still responded well to plasmapheresis with or without rituximab supports that the initial triggering event is not the putative circulating factors *per se* and is likely B-cell independent.

Beyond plasmapheresis and rituximab, low-density lipoprotein (LDL) apheresis has been evaluated as a preventive strategy for recurrent FSGS in a Japanese study[49]. LDL apheresis removes plasma lipids, a source of oxidative stress, as well as multiple circulating humoral factors that contribute to disease recurrence. The authors reported no FSGS recurrence in five patients using this regimen of pre-transplant LDL apheresis, in addition to rituximab and basiliximab induction; however, this finding should be confirmed by larger studies.

The results of this meta-analysis should be interpreted with attention to the study limitations. First, all included studies were observational in design; thus, the risk of

Table 4 Detailed characteristics of included studies evaluating the outcomes of preemptive rituximab

Ref.	Country	Age	Genetic testing	Race	Time to ESKD	Repeat KT	Induction	IS	DDKT	Follow-up duration
Burke *et al* [22], 2009	United States	Age at KT: 6-21 yr	N/A	N/A	N/A	N/A	rATG or daclizumab	CS, Tac, MMF	N/A	N/A
Sagheshima *et al*[23], 2010	United States	Age at KT: 4-24 yr	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fornoni *et al* [24], 2011	United States	Age at KT: 15 ± 5.5 yr (rituximab), 12.3 ± 5.2 yr (control)	N/A	White 56%, Black 44%	3.4 ± 2.0 yr (rituximab group), 3.3 ± 2.1 (control)	N/A	Combined thymoglobulin (1 mg/kg, 3–5 doses) and daclizumab. Alemtuzumab in one patient.	CS, Tac, MMF	Preemptive: 3/27 (11%) in rituximab group, 2/14 (14%) in non-rituximab group	N/A
Miyauchi *et al* [25], 2011	Japan	FSGS undergoing KT	N/A	Asian	N/A	N/A	N/A	CS, CsA/Tac, AZA/mizolibine	N/A	N/A
Park *et al*[26], 2014	South Korea	Age at KT: 39 ± 14 (n = 7, recurrence), 36 ± 11 (n = 20, no recurrence)	N/A	Asian	46 ± 44 mo (n = 7, recur group), 68 ± 67 mo (n = 20, no recur group)	none	Basiliximab (20 mg) on days 0 and 4	CS, CsA/Tac, MMF	3/27 DDKT, 24/27 living	N/A
Okumi *et al* [27], 2015	Japan	N/A	N/A	Asian	N/A	N/A	Basiliximab (after 2002)	CS, CsA/Tac, MMF	N/A	N/A
Futamura *et al* [28], 2016	Japan	N/A	N/A	Asian	N/A	N/A	N/A	N/A	N/A	N/A
Alasfar *et al* [29], 2018	United States	Age at FSGS Dx: 29.9 ± 17.2. Age at KT: 38 ± 16.5	N/A	White 56%, Black 32%, Asian 7%, Hispanic 4%	4 (0–9) yr	37% (42/66 63% first transplant)	Depleting agent 92%	CS + Tac + MMF (92%), CS + CsA + MMF (8%)	DDKT 37%, LUKT 37%, LRKT 25%	29.5 mo
Lu *et al*[30], 2018	United States	Age at KT: 44	N/A	White 64%	N/A	0%	N/A	CS, Tac, MMF	N/A	N/A
Auñón *et al* [31], 2021	Spain	Age at FSGS Dx: 24.5 ± 18.5 (rituximab group), 30 ± 13.7 (non-rituximab group). Age at KT: 35.0 ± 15.2 (R group), 42.4 ± 12.2 (non-R group)	Excluded suspected genetic causes of FSGS	N/A	5.12 ± 4.44 (R group), 7.58 ± 7.11 (Non-R group)	7/34 (21%); recurrence in previous graft 2/12 (16.7%) in R group *vs* 2/22 (9.1%) In non-R group	Rituximab group: rATG 16.7%, basiliximab 50%. Non-rituximab group: rATG 40.9%, basiliximab 22.7%	CS + Tac + MMF (93.3%)	85.3% DDKT, 11.8% LRKT, 2.9% LUKT	N/A
Mukku *et al* [39], 2021	United States	Age at KT: 35 yr	N/A	White 39%, Black 27%	N/A	2/8 pre-emptive group *vs* 0/10	rATG (61%), alemtuzumab (22%), basiliximab (17%)	CS + Tac + MMF (83%), CS + CsA + MMF (17%)	89% DDKT	30 (1-36) mo

N: Number; ESKD: End-stage kidney disease; FSGS: Focal segmental glomerulosclerosis; RRT: Renal replacement therapy; PP: Plasmapheresis; IS: Immunosuppression; KT: Kidney transplantation; RTX: Rituximab; CS: Corticosteroids; CsA: Cyclosporine; Tac: Tacrolimus; MMF: Mycophenolate mofetil; AZA: Azathioprine; rATG: Rabbit anti-thymocyte globulin; DDKT: Deceased donor kidney transplantation; LRKT: Living-related kidney transplantation; LUKT: Living-related kidney transplantation; N/A: Not available.

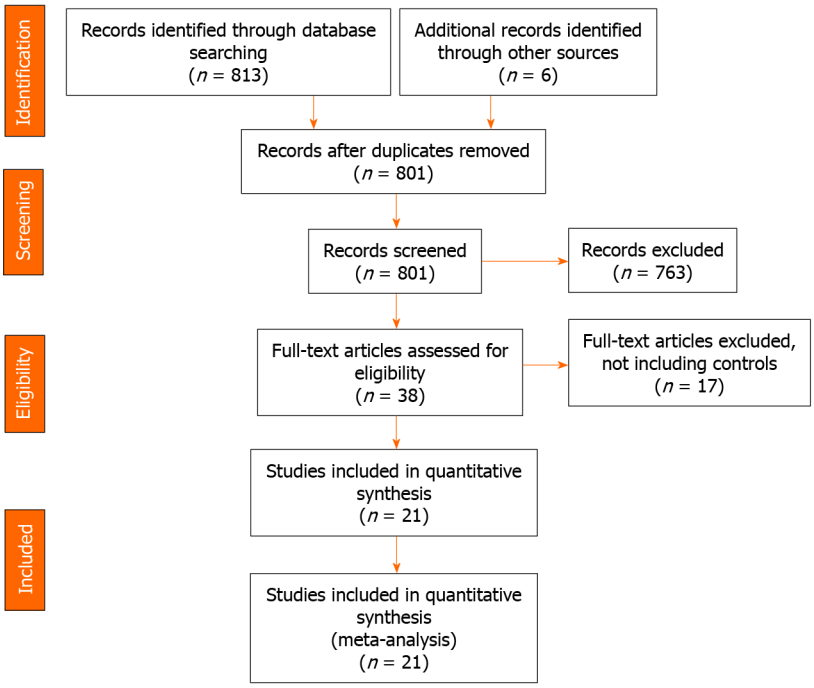

Figure 1 Outline of search methodology, PRISMA 2009 flow diagram.

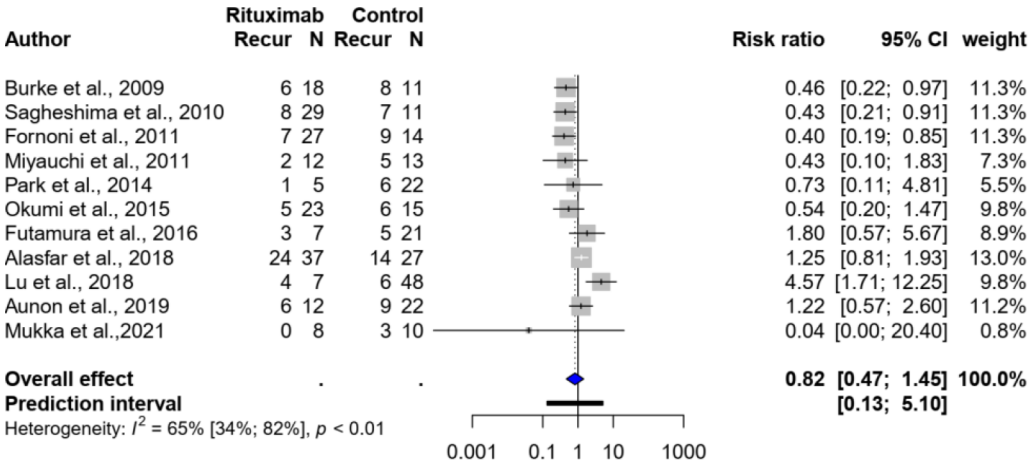

Figure 2 Pooled risk ratio of focal segmental glomerulosclerosis recurrence between the group that received rituximab (with or without plasmapheresis) and the standard treatment group.

bias was present, and causality could not be established. Second, the sample size of most studies was small. Third, some studies did not report patient characteristics or prognostic factors. Fourth, the treatment regimen, dose of rituximab, and plasmapheresis protocol (frequency, duration, and volume of exchange) were not standardized. Fifth, the use of induction and background immunosuppression varied across studies, depending on the institutional protocol and era of medication availability. Finally, as evidenced by the widely varying recurrence risks reported, it is possible that the different studies enrolled FSGS patients with inherently varying risk of recurrence, resulting in further difficulties regarding the interpretation of post-transplant risk; the eligibility criteria were heterogeneous.

Efforts to elucidate the pathogenic mechanisms of FSGS are ongoing. Further clinical research is therefore required, both to accurately identify the subgroup of patients with FSGS who are at a higher risk for disease recurrence, as well as evaluate preventive interventions within this subgroup. At the time of writing, one ongoing randomized controlled trial (clinical trial number: NCT03763643) was identified, with the primary endpoint of preventing recurrent FSGS through the use of preemptive rituximab plus plasmapheresis or plasmapheresis alone.

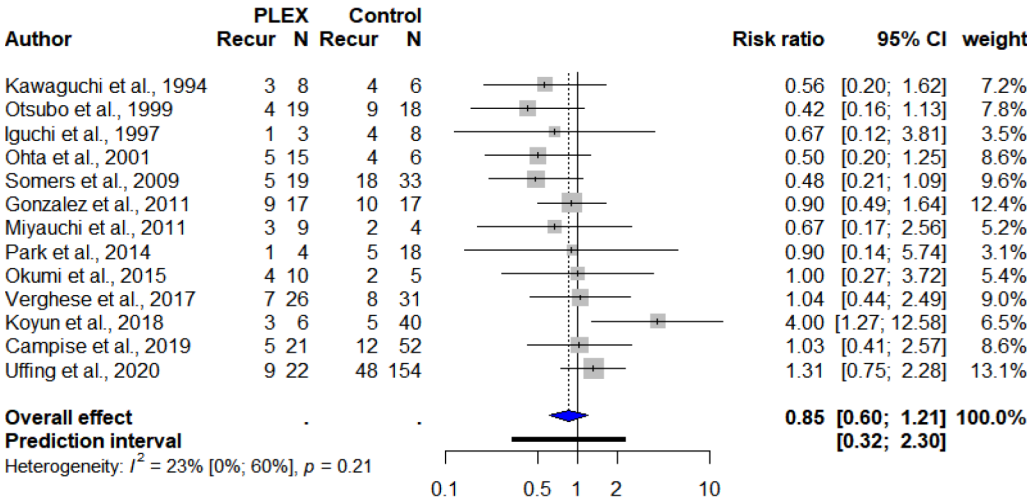

Figure 3 Pooled risk ratio of focal segmental glomerulosclerosis recurrence between patients who did and did not receive plasmapheresis.

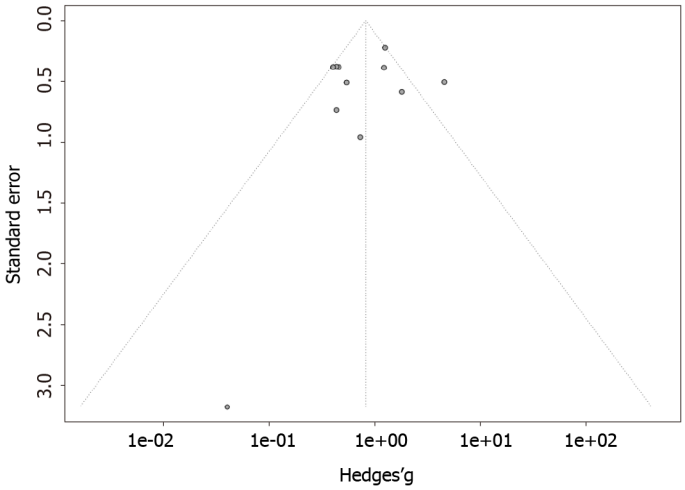

Figure 4 Funnel plot evaluating publication bias regarding the effects of rituximab on focal segmental glomerulosclerosis recurrence.

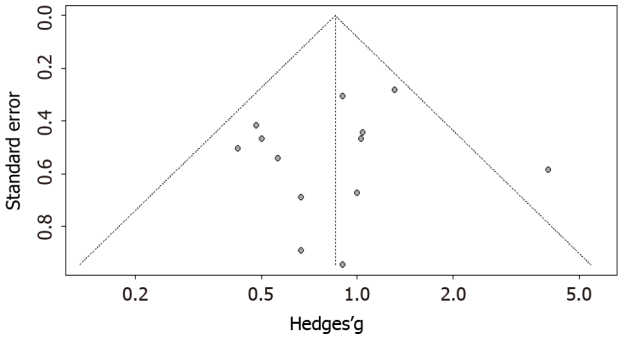

Figure 5 Funnel plot evaluating publication bias regarding the effects of plasmapheresis on focal segmental glomerulosclerosis recurrence.

CONCLUSION

In unselected patients with FSGS, preemptive rituximab with or without plasmapheresis, or plasmapheresis alone, was not associated with a lower risk of FSGS recurrence after kidney transplantation.

ARTICLE HIGHLIGHTS

Research background

Focal segmental glomerulosclerosis (FSGS) is one of the most common glomerular diseases leading to kidney failure. FSGS has a high risk of recurrence after kidney transplantation. Prevention of recurrent FSGS using rituximab and/or plasmapheresis has been evaluated in multiple small studies with conflicting results.

Research motivation

FSGS is associated with a high risk of recurrence after kidney transplantation. Plasmapheresis and/or rituximab has been used to prevent recurrence with conflicting results.

Research objectives

This meta-analysis was conducted to assess the effectiveness of rituximab–with or without plasmapheresis–compared with plasmapheresis alone, for the prevention of recurrent FSGS after kidney transplantation.

Research methods

This meta-analysis and systematic review were performed by first conducting a literature search of the MEDLINE, EMBASE, and Cochrane databases, from inception through March 2021; search terms included 'FSGS', 'steroid-resistant nephrotic syndrome', 'rituximab', and 'plasmapheresis'. We identified studies that assessed the risk of post-transplant FSGS after use of rituximab with or without plasmapheresis, or plasmapheresis alone.

Research results

Eleven studies, with a total of 399 kidney transplant recipients with FSGS, evaluated the use of rituximab with or without plasmapheresis; thirteen studies, with a total of 571 kidney transplant recipients with FSGS, evaluated plasmapheresis alone. Post-transplant FSGS recurred relatively early. There was no significant difference in recurrence between the group that received rituximab (with or without plasmapheresis) and the standard treatment group, with a pooled risk ratio of 0.82 [95% confidence intervals (CI): 0.47-1.45]. Similarly, plasmapheresis alone was not associated with any significant difference in FSGS recurrence when compared with no plasmapheresis; the pooled risk ratio was 0.85 (95%CI: 0.60-1.21). Subgroup analyses in the pediatric and adult groups did not yield a significant difference in recurrence risk. We also reviewed and analyzed post-transplant outcomes including timing of recurrence and graft survival.

Research conclusions

The use of rituximab with or without plasmapheresis, or plasmapheresis alone, is not associated with a lower risk of FSGS recurrence after kidney transplantation.

Research perspectives

This meta-analysis is among the first to report that the use of preemptive rituximab, either alone or in combination with plasmapheresis, or plasmapheresis alone, did not alter the recurrence risk of FSGS after kidney transplantation.

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