OPEN

Combined Anti-CD20/Anti-CD38 Therapy in Posttransplant Focal Segmental Glomerulosclerosis Recurrence: A Retrospective, International, Multicenter Study

Paolo Cravedi, MD, PhD,[1] Umberto Maggiore, MD, PhD,[2] Gabriele Mortari, MD,[3] Federico Alberici, MD, PhD,[4,5] Gaetano La Manna, MD, PhD,[6,7] Nelson Goes, MD,[8] Nicolas Bouvier, MD,[9] Giorgia Comai, MD, PhD,[6,7] Ali Poyan Mehr, MD,[8] Micaela Gentile, MD,[2] Alessandra Palmisano, MD,[2] Elisa Gessaroli, MD,[6,10] Simona Barbuto, MD,[6,7] Gianluca Caridi, BSc,[3] Carolina Bigatti, MD,[1,3] Alberto Magnasco, MD,[3] Nicola Bossini, MD,[4] Xhuliana Kajana, BSc,[3] Agnese Spennacchio, BSc,[3] Lorenzo Gallon, MD, PhD,[10] Gian Marco Ghiggeri, MD,[3] Flavio Vincenti, MD,[11,12] Frank E. Hullekes, MD,[13] Rohan V. Mehta, MD,[14] Leonardo V. Riella, MD, PhD,[13] Enrico E. Verrina, MD,[3] and Andrea Angeletti, MD, PhD[3]

Background. Focal segmental glomerulosclerosis (FSGS) recurrence after kidney transplantation is a leading cause of allograft failure and remains difficult to treat. Standard therapies, including plasma exchange (PEX) and rituximab, are often ineffective and poorly tolerated. Growing evidence implicates immune-mediated circulating factors, such as IgG and IgM autoantibodies, in disease pathogenesis. Given the central role of memory B cells and plasma cells in antibody production, we tested the safety/efficacy profile of a combined B-cell and plasma cell–depleting approach with rituximab and daratumumab in patients with posttransplant FSGS recurrence. **Methods.** This is a retrospective analysis of a multicenter, international cohort of sixteen patients (median age 37 y) with biopsy-proven FSGS recurrence posttransplant who received anti-CD20 plus anti-CD38 monoclonal antibodies or anti-CD38 alone. The majority of patients were resistant to common therapies, including rituximab and PEX. **Results.** The treatment achieved complete or partial remission in 5 and 11 patients, respectively. Five experienced proteinuria relapse, and 4 responded to repeated daratumumab alone. At the last follow-up (median 11 [2–18] mo), 13 patients are still in remission and PEX was discontinued in all but 3 cases. Overall, kidney function improved after treatment, and no severe acute or chronic adverse events were reported. Serological analysis revealed a significant decline in IgM, but not in IgG, after treatment. **Conclusions.** Despite the retrospective, nonrandomized design, the temporal association between treatment and remission supports an effect of anti-CD38 monoclonal antibody alone or in combination with anti-CD20. Treatment is safe and may confer enhanced efficacy over standard approaches. Prospective, mechanistic studies are warranted to validate these findings and delineate the immunopathogenesis of FSGS recurrence.

(*Transplantation Direct* 2026;12: e1908; doi: 10.1097/TXD.0000000000001908.)

Received 18 November 2025.

Accepted 4 December 2025.

[1] *Department of Medicine, Transplantation Research Center, Icahn School of Medicine at Mount Sinai, New York, NY.*

[2] *Nephrology Unit, University Hospital of Parma, Parma, Italy.*

[3] *Nephrology, Dialysis and Transplantation Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy.*

[4] *Division of Nephrology and Dialysis, Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili de Brescia, Brescia, Italy.*

[5] *Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy.*

[6] *Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna, Italy.*

[7] *Nephrology, Dialysis and Kidney Transplant Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy.*

[8] *Department of Nephrology, Kaiser Permanente San Francisco Medical Center, San Francisco, CA.*

[9] *Department of Nephrology and Transplantation, University of Caen, Caen, France.*

[10] *Division of Nephrology, Department of Medicine, University of Illinois College of Medicine, Chicago, IL.*

[11] *Kidney Transplant Service, Department of Medicine, University of California-San Francisco, San Francisco, CA.*

[12] *Kidney Transplant Service, Department of Surgery, University of California-San Francisco, San Francisco, CA*

[13] *Center for Transplantation Sciences, Massachusetts General Hospital, Harvard Medical School, Boston, MA.*

[14] *Division of Nephrology, Hypertension and Renal Transplantation, Department of Medicine, College of Medicine, University of Florida, Gainesville, FL.*

A.A. and G.C. were supported by the European Union – Next Generation EU – NRRP M6C2 – Investment 2.1 Enhancement and strengthening of biomedical research in the NHS.

The authors declare no conflicts of interest.

A.A. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. A.A. participated in concept and design. A.A., G.C., X.K., C.B., G.M., U.M., F.A., G.C., N.B., N.G., A.P.M., M.G., A.P., E.G., S.B., N.B., L.G., F.E.H., R.V.M., and L.V.R. participated in acquisition, analysis, or interpretation of data. A.A. and P.C. participated in drafting the article. A.A., P.C., F.V., L.V.R., L.G., E.E.V., G.M.G., U.M., and G.L.M.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) represents one of the major causes of kidney failure. The disease often recurs after kidney transplantation, affecting approximately 30%–40% of patients, and is associated with poor graft survival, accelerated graft loss, and significant morbidity.[1,2] Effective management of recurrent FSGS remains a significant clinical challenge due to limited therapeutic options and a poor understanding of its underlying pathophysiological mechanisms. Current therapeutic approaches for recurrent FSGS primarily include plasma exchange (PEX) and rituximab, a monoclonal antibody targeting the CD20 antigen expressed on B cells.[3] However, the effectiveness of these interventions is inconsistent, and prolonged use of PEX is often poorly tolerated.

The pathophysiology of FSGS recurrence remains largely unknown, but current understanding implies the presence of immune-derived circulating factors, including anti-nephrin IgG and natural IgM antibodies.[4,5] Because memory B cells and plasma cells represent the major sources of antibodies, we tested the safety/efficacy profile of combined anti-CD20 and anti-CD38 depletion treatments in FSGS recurrence. In our initial case series involving 5 patients with recurrent FSGS posttransplant, we demonstrated that a novel therapeutic combination of rituximab (anti-CD20) and daratumumab (anti-CD38), targeting B cells and plasma cells, respectively, safely and effectively induced disease remission.[6] Following the promising results of this pilot study, numerous transplantation centers internationally have adopted this combined therapeutic approach.[7,8]

In the present study, we extend our initial observations through a multicenter, international retrospective cohort analysis encompassing 16 additional patients who experienced FSGS recurrence after kidney transplantation and were treated with either the combination regimen of anti-CD20 plus anti-CD38 monoclonal antibodies or anti-CD38 alone. By expanding both the sample size and geographic diversity of the cohort, we aim to further assess the safety and efficacy of this targeted immunotherapy. Additionally, this larger and more diverse data set provides an opportunity to identify potential biomarkers predictive of therapeutic response, thereby contributing to our understanding and management of recurrent FSGS.

MATERIALS AND METHODS

Study Design and Population

This was a retrospective, international, multicenter study aimed to establish the effects of treatment with rituximab, a chimeric monoclonal anti-CD20 antibody; obinutuzumab, a humanized glycoengineered type II anti-CD20 monoclonal antibody; and daratumumab, a fully human monoclonal anti-CD38 antibody, in kidney transplant recipients with FSGS recurrence. Patients were enrolled in the following Centers: Nephrology Unit, University Hospital of Parma, Parma, Italy (n = 3); Division of Nephrology, Hypertension and Renal Transplantation, University of Florida, Gainesville, FL (n = 3); Giannina Gaslini Institute, Genoa, Italy (n = 2); Division of Nephrology and Dialysis, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy (n = 2); Nephrology, Dialysis and Kidney Transplant Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy (n = 3); Department of Nephrology and Transplantation, University of Caen, Caen, France (n = 1), Kidney Transplant Clinics, Kaiser Permanente, San Francisco, CA (n = 1); Center for Transplantation Sciences, Massachusetts General Hospital, Boston, MA (n = 1). In these Centers, all consecutive patients with a diagnosis of FSGS recurrence and treated with anti-CD20 plus anti-CD38 monoclonal antibodies or anti-CD38 alone from January 2024 to April 2025 were included in our analyses. All patients with biopsy-proven recurrent FSGS who received combined anti-CD20 and anti-CD38 monoclonal antibodies at the participating centers were included, without any selection based on clinical stability or disease severity. Recurrence was confirmed by transmission electron microscopy, showing predominant podocyte effacement.

All patients or their relatives (for patients younger than 18 y) provided written informed consent before enrollment, and all treatments were administered in accordance with local regulations and with the requirements of the respective local Ethics Committees, where applicable. The protocol was approved by the IRCCS Giannina Gaslini Institute (Genoa, Italy) ethics committee (CBUF-IGG2023), and all patients or relatives (in case of patients younger than 18 y) provided written informed consent before enrollment, in compliance with local regulations. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Clinical Data Collection

Clinical data were extracted from the electronic medical records. Eligible patients were identified using International Classification of Diseases codes, procedure codes, and/or pharmacy records as appropriate.

Data collected included demographics (age, sex, race/ethnicity), relevant comorbidities, baseline laboratory values, immunosuppression, and outcome measures. Adverse events were identified through clinical documentation, laboratory results, and discharge diagnoses.

All data were entered into a secure, de-identified database.

Anti-CD20 and Anti-CD38 Monoclonal Antibodies Infusion

Patients received premedication with intravenous methylprednisolone (2 mg/kg diluted in 100 mL of normal saline in 30 min), oral cetirizine (0.2 mg/kg), and oral paracetamol (15 mg/kg), to reduce the risk of infusion reactions. Rituximab

participated in critical review of the article for important intellectual content. A.A. participated in supervision.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Andrea Angeletti, MD, PhD, Nephrology, Dialysis and Transplantation, Istituto Giannina Gaslini, Via Gaslini 5, 16147, Genoa, Italy (andreaangeletti@gaslini.org).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001908

was administered as a single dose of 375 mg/m^2 diluted in saline. For doses <500 mg, rituximab was diluted in 250 mL of normal saline and administered at 6 mL/h for the first 30 min, 9 mL/h for the next 30 min, 18 mL/h for the subsequent 30 min, and then 36 mL/h until the end of the infusion. For doses between 500 and 1000 mg, rituximab was diluted in 500 mL of normal saline and administered at 9 mL/h for the first 30 min; thereafter, the infusion rate was doubled every 30 min up to a maximum of 72 mL/h.

Obinutuzumab (Roche, Basel, Switzerland) was infused intravenously at a dose of 1000 mg. Obinutuzumab was diluted in 500 mL of normal saline and administered at 9 mL/h for the first 30 min; thereafter, the infusion rate was doubled every 30 min up to a maximum of 72 mL/h.

Daratumumab was infused around 15 d after the anti-CD20 monoclonal antibody. Patients received a premedication with methyl-prednisolone (2 mg/kg diluted in 100 mL of normal saline, infused intravenously over 30 min), oral cetirizine (0.2 mg/kg), and oral paracetamol (15 mg/kg). After 2 h from the start of infusion, patients received a second medication with methyl-prednisolone (20 mg diluted in 50 mL of normal saline) and oral cetirizine (0.2 mg/kg). Daratumumab was administered as a single dose of 16 mg/kg diluted in 1000 mL of saline. Daratumumab was administered at 9 mL/h for the first 30 min; thereafter, the infusion rate was doubled every 30 min up to a maximum of 100 mL/h.

No prophylaxis against any type of viral or bacterial infections was administered before anti-CD20 or anti-CD38 infusions. As per protocol in the various centers, antirejection treatment based on steroids, mycophenolate mofetil, and calcineurin inhibitors was not modified after diagnosis of FSGS recurrence.

Response to Treatment

Response to treatment was defined according to the Kidney Disease: Improving Global Outcomes guidelines.[9] Complete remission was defined as an albumin/creatinine ratio (ACR) < 0.300 g/g and partial remission was defined as ACR >0.3 g/g but <3.5 g/g or a decrease in proteinuria by ≥50% from the initial value and ACR <3.5 g/g. Relapse was defined as ACR >3 g/g after an initial remission.

Immunoprecipitation for Anti-Nephrin IgG

The presence of anti-nephrin autoantibodies was determined by immunoprecipitation, as previously reported[10] and as described in **Supplemental Material and Figure S1** (**SDC,** https://links.lww.com/TXD/A823).

Statistical Analyses

Continuous variables were expressed as mean ± SD or as median and interquartile range, depending on data distribution. Group comparisons for continuous variables were performed using the paired *t*-test or Wilcoxon signed-rank test, as appropriate. Normality of distribution was assessed using the Shapiro-Wilk test. Relapse-free survival was estimated using the Kaplan-Meier method, and differences between groups were evaluated with the log-rank (Mantel-Cox) test. All *P* values were 2-sided, and a value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 10 (GraphPad Software, San Diego, CA).

RESULTS

Baseline Characteristics

The baseline characteristics of the sixteen patients included in this study are summarized in Table 1. The cohort consisted of 5 women and 11 men, with a median age of 37 y (range, 6–58 y), all of whom received a non–preemptive deceased-donor kidney transplant. All patients had biopsy-proven recurrence of FSGS after kidney transplantation, and 14 of 16 were undergoing PEX at the time of recurrence. No patients required renal replacement treatment due to the recurrence. Anti-nephrin IgG antibodies were measured in 2 patients (patient 3 and patient 8) at the time of recurrence, before any plasma exchange or anti-CD20 treatment, with both tests returning negative results. Genetic test for monogenic cause of FSGS (**Supplemental Material, SDC,** https://links.lww.com/TXD/A823), performed in 7 patients, was negative (Table 1).

Treatment Efficacy

Overall, treatment significantly reduced proteinuria during the first 4 mo after treatment (time of the patient with the shortest follow-up period; Figures 1 and 2A). Nine patients achieved complete remission and 5 patients partial remission (Figure 1). Within 2 to 5 mo posttreatment, 4 patients experienced a relapse and subsequently received daratumumab monotherapy. Of these, 3 achieved remission, whereas 1 did not respond to treatment (Figure 1).

At the last follow-up visit at a median of 11 mo (range, 2–18 mo) after inclusion, 15 patients remained in partial (n = 5) or complete (n = 10) remission. PEX sessions were discontinued in 11 of 15 patients. Patient 9, who did not respond to the second daratumumab treatment, started PEX treatment after inclusion in the study. Kidney function remained stable throughout the follow-up period (Figure 2B).

Patient 4 and patient 14 failed to respond to rituximab alone and were treated with daratumumab alone >6 mo after their last rituximab infusion, achieving partial and complete remission, respectively.

Response to Treatment in Relation to Timing of Treatment

Patients received treatment either early (within 12 mo; N = 7) or late (after 12 mo; N = 9) following posttransplant FSGS recurrence. To evaluate whether treatment timing influenced clinical outcomes, we compared the requirement for additional therapy between the 2 groups. As shown in Figure 2C, all patients treated within the first 12 mo achieved and maintained stable remission, suggesting enhanced efficacy with early intervention, confirming previous findings.

Changes in Antibodies and Other Serum Parameters

After treatment, total IgM significantly declined, whereas IgG did not significantly change (Figure 2D and E). However, the level of circulating IgM after the initial infusions did not correlate with the risk of proteinuria relapse and the subsequent need for additional daratumumab infusions (data not shown). All other tested biochemical parameters, including serum albumin and lipid profile, changed in accordance with the reduction in proteinuria and were not associated with the risk of proteinuria relapse (not shown).

TABLE 1.

Baseline characteristics of patients

Patient No.	Age, sex	Genetic	sAlb, g/dL	eGFR, mL/min/1.73 m²[a]	IgG, mg/dL	IgM, mg/dL	Previous RTX	Time since last RTX, mo	PEX Regimen,[b] N/wk	Previous KT	Induction	IS regimen[b]	RAASi
Pt 1	57, M		2.7	36	NA	NA	0		2	0	Anti-IL2R	CNI, MMF, Ste	Y
Pt 2	21, M	NEG	2.9	74	382	48	2	22	1	0	Anti-IL2R	CNI, MMF, Ste	Y
Pt 3	46, F	NEG	2.3	46	656	199	4	38	2	0	Anti-IL2R	CNI, MMF, Ste	N
Pt 4	29, M	NEG	3.4	59	NA	NA	1	10	1	1	Thymo	CNI, MMF, Ste	Y
Pt 5	58, M		2.9	62	154	98	0		3	1	Thymo	CNI, MMF, Ste	Y
Pt 6	43, M	NEG	3.3	36	NA	NA	0		0	3	Thymo	CNI, MMF, Ste	N
Pt 7	37, M		4	43	144	10	4	9	3	0	Anti-IL2R	CNI, MMF, Ste	Y
Pt 8	6, M	NEG	3.2	102	614	84	0		3	0	Anti-IL2R	CNI, MMF, Ste	Y
Pt 9	23, M	NEG	4	11	NA	NA	0		2	2	Thymo	CNI, MMF, Ste	Y
Pt 10	51, F		2.2	62	257	19	1	8	3	2	Thymo	CNI, MMF, Ste	Y
Pt 11	54, F		3.4	23	397	20	2	11	2	0	Thymo	CNI, MMF, Ste	N
Pt 12	75, F		NA	51	NA	NA	1	10	0	0	Anti-IL2R	CNI, MMF, Ste	Y
Pt 13	59,M		4.2	90	960	87	0		0	0	Thymo	CNI, MMF, Ste	Y
Pt 14	44, F		3.2	41	325	22	3	21	1	0	Thymo	CNI, MMF, Ste	N
Pt 15	35,F	NEG	3.1	87	NA	NA	0		3	1	Thymo	CNI, MMF, Ste	Y
Pt 16	43, M		2.9	47	NA	NA	0		3	0	Anti-IL2R	CNI, MMF, Ste	Y

[a]eGFR was calculated using the CKD-EPI or Schwartz formula, according to age.

[b]CNI consisted of tacrolimus (FK) or cyclosporine. Target trough levels for tacrolimus were 5–7 ng/mL, whereas cyclosporine target levels were 100–150 ng/mL (C0) or 600–800 ng/mL (C2), depending on the posttransplant period and in accordance with each center's protocol. PEX sessions involved an exchanged plasma volume of approximately 1.5 times the patient's estimated plasma volume and were discontinued for at least 1 wk after monoclonal antibody infusions to minimize the risk of drug removal.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CNI, calcineurin inhibitor; IL2R, interleukine-2 receptor; IS, immunosuppressive; KT, kidney transplant; MMF, mycophenolate mofetil; NEG, negative; PEX, plasma exchange; RAASi, renin–angiotensin–aldosterone system inhibitors; RTX, rituximab; sAlb, serum albumin; Ste, steroid.

Treatment Safety

No serious adverse events were reported during treatment. Mild infusion-related reactions, including subjective dyspnea and pruritus, occurred in 4 patients; however, symptoms promptly resolved after brief interruption of the infusion, and treatment was completed in all cases. One patient developed BK virus viremia 1 mo after initiating combined therapy, which was successfully managed by discontinuing mycophenolate mofetil.

DISCUSSION

Posttransplant recurrence of FSGS is a significant challenge in kidney transplantation, often leading to rapid graft loss due to limited effective therapeutic options.[1] In this international, multicenter retrospective study, we evaluated the safety and efficacy of adding daratumumab, an anti-CD38 monoclonal antibody targeting plasma cells, to the conventional treatments, including anti-CD20 monoclonal antibody and PEX.[3] Our findings demonstrated that this combined therapy is generally well tolerated and achieves remission of proteinuria in most patients.

Importantly, we observed that early administration of combined therapy, particularly within 12 mo postrecurrence, was associated with sustained remission and reduced need for additional treatments. This temporal stratification of treatment outcomes underscores the potential importance of early therapeutic intervention. Furthermore, the favorable outcomes observed in this expanded cohort reinforce the promising results of our initial case series,[6] suggesting that combined rituximab-daratumumab treatment may offer superior clinical benefits compared with standard approaches.[7,8]

The exact pathogenesis of recurrent FSGS remains unclear, although growing evidence supports the involvement of antibody-mediated mechanisms. IgG autoantibodies targeting nephrin and other components of the glomerular slit diaphragm have been identified in subsets of patients, and their pathogenic role has been validated experimentally.[4,11-13] Moreover, IgM deposits are frequently observed in glomerular lesions of patients with FSGS.[14] Although traditionally considered passive entrapment, recent data suggest active binding of natural IgM to neoantigens exposed by damaged glomerular endothelial cells, including cardiolipin.[5,15] This leads to the activation of the classical complement pathway, which promotes the formation of the complement split product C3a, which binds to its receptor (C3aR) on podocytes, leading to cytoskeletal rearrangement and podocyte loss.[16] Our prior[17] and present data suggest a possible association between IgM levels after combined therapy and disease activity (Figure 2b), supporting, although not formally proving, this working model.[7] However, in our cohort, the levels of circulating IgM were not monitored serially, and we could not formally test an association with proteinuria relapse. Further ad hoc studies are needed to establish the role of autoreactive IgG and IgM in the pathogenesis of FSGS. Defining the role of autoantibodies may help in refining therapies and biomarkers of disease activity.[18,19]

Prospective controlled trials are urgently needed to confirm the efficacy and safety of combined B-cell and plasma cell–targeted therapy. If the favorable safety profile observed in our cohort were confirmed, this approach could be reasonably extended to all patients with recurrent FSGS, given the severity of the disease and its critical impact on graft survival. Future studies should aim to define clinical, serological, or histological markers that may help identify patients most likely to benefit from dual or sequential therapy.

Despite these promising findings, several caveats should be considered when interpreting our results. The retrospective,

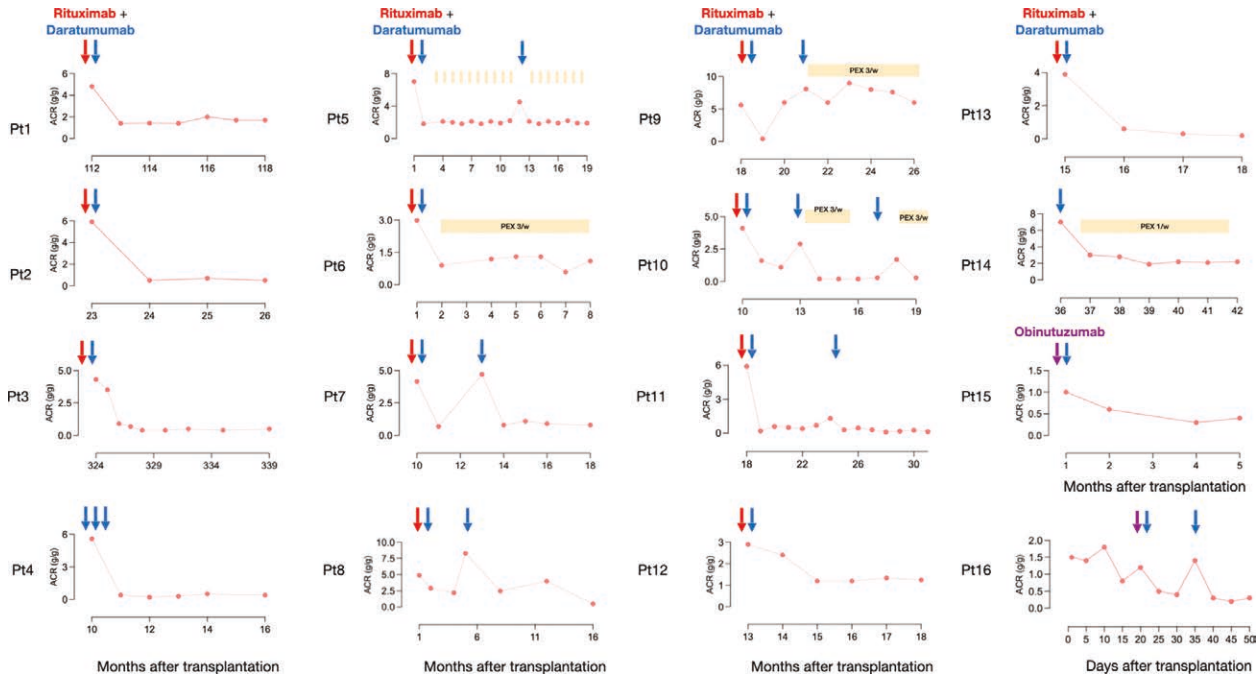

FIGURE 1. Detailed response to treatment with combined rituximab and daratumumab in FSGS recurrence after KT. ACR levels after combined rituximab + daratumumab for each patient. ACR, albumin/creatinine ratio; FSGS, focal segmental glomerulosclerosis; KT, kidney transplant.

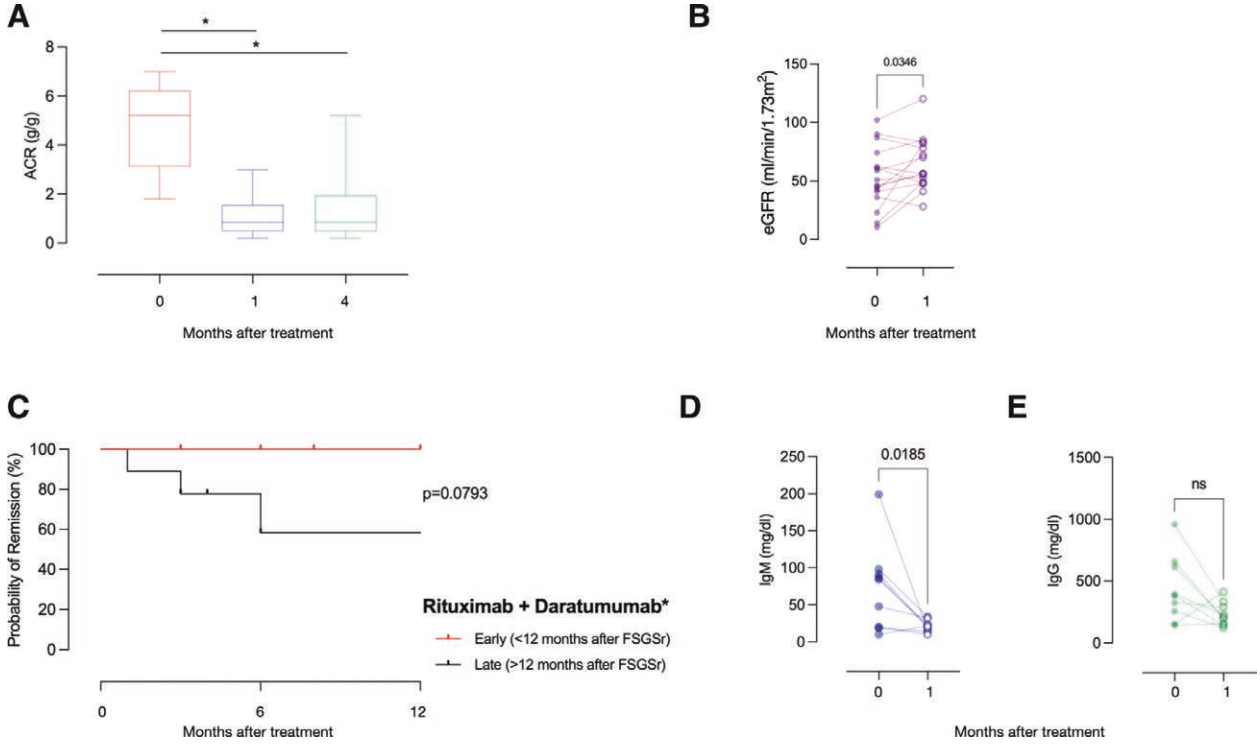

FIGURE 2. Overall response and time relevance of the combined treatment. A, Overall ACR (g/g) at t_0 was 4.8 on average (range, 1.8–7), at 1 mo (t_{1m}) was 1.1 on average (range, 0.2–3), and at 4 mo (t_{4m}) was 1.3 on average (range, 0.2–5.2). B, Overall eGFR at baseline and at t_{1m} after treatment. C, Comparison between kidney transplant recipients treated within (n = 7) and after (n = 9) the first 12 mo post-FSGS recurrence. D and E, Overall circulating IgM (mg/dL) and IgG (mg/dL) at baseline and at 1 mo after combined rituximab + daratumumab (serum level of IgM and IgG were available in 9 patients). *Two patients received only daratumumab. ACR, urinary albumin/creatinine ratio (g/g); eGFR, estimated glomerular filtration rate was calculated on the basis of the Chronic Kidney Disease Epidemiology Collaboration formula or the Schwartz formula, according to age; FSGS, focal segmental glomerulosclerosis; PEX, plasma exchange.

uncontrolled nature of this study inherently limits the ability to draw definitive conclusions regarding causality. Nevertheless, spontaneous remission in recurrent FSGS is exceedingly uncommon,[1] thereby making the observed temporal relationship between treatment initiation and disease remission highly suggestive of a true therapeutic effect. Furthermore, given the study design, it is challenging to distinctly evaluate the relative contributions of anti-CD20 and anti-CD38 monoclonal antibodies to clinical improvement.

The observation that some patients previously unresponsive to anti-CD20 therapy achieved remission with anti-CD38 monotherapy suggests that plasma cell–driven mechanisms may play a dominant role in certain cases of recurrent FSGS. Our recent data in patients with steroid-resistant nephrotic syndrome[20,21] document that depletion of $CD38^+$ B cells represents a predictor of response to therapy, suggesting that daratumumab alone may suffice, at least in some patients.

Because most patients received rituximab and only 2 were treated with obinutuzumab, the study is underpowered to compare different anti-CD20 agents or to infer the superiority of any specific regimen. Two patients in our cohort received obinutuzumab instead of rituximab as the anti-CD20 agent. Obinutuzumab is a humanized glycoengineered type II anti-CD20 monoclonal antibody that, unlike rituximab, which primarily relies on complement-dependent cytotoxicity, produces more profound B-cell depletion through enhanced direct cell apoptosis and antibody-dependent cellular cytotoxicity.[22,23] Preliminary data from native kidney disease suggest that obinutuzumab may provide more sustained B-cell depletion in multirelapsing forms of FSGS;[24] however, its safety and efficacy in kidney transplant recipients with FSGS recurrence remain to be established in future studies.

Notably, CD38 is broadly expressed on various immune cell types, including activated conventional and unconventional T cells, natural killer (NK) cells, monocytes, and macrophages.[25] Therefore, although plasma cell depletion is the most straightforward and biologically plausible explanation for the therapeutic effect, we cannot formally exclude the possibility that remission may also result from the depletion or functional modulation of these other immune subsets. As NK cells express CD38, their modulation during treatment would be of interest; however, NK cell counts were not systematically collected in our cohort, which represents a limitation of the study.

Anti-nephrin antibodies were assessed in 2 patients at the time of recurrence, before any plasma exchange or anti-CD20 therapy, and both tested negative. The very limited number of tested cases does not allow any conclusions to be drawn regarding their potential role in disease recurrence. Therefore, additional mechanistic studies are warranted to precisely define the cellular targets of daratumumab and their potential contributions to the pathogenesis and treatment response in recurrent FSGS. Due to the retrospective and multicentric design, detailed immunological data, including deep immunephenotype or biopsy staining for IgG antibodies, were not consistently available and represent a limitation of this study.

The treatment was well tolerated. However, adverse events were retrospectively collected from medical records; therefore, milder or subclinical events may have been underreported, representing a limitation of this study.

In conclusion, this multicentre retrospective study suggests that combined B-cell and plasma cell–targeted therapy may represent a safe and effective option for recurrent FSGS after kidney transplantation. Nonetheless, treatment heterogeneity, including prior rituximab exposure and the use of obinutuzumab in 2 cases, and the retrospective design, warrant cautious interpretation. Prospective, randomized studies are needed to confirm these findings and clarify the underlying mechanisms.

ACKNOWLEDGMENTS

The authors thank all the nurses and the physicians of the Operative Units, whose dedication, professionalism, and compassionate care greatly facilitate our clinical and research activities.

REFERENCES

1. Uffing A, Perez-Saez MJ, Mazzali M, et al. Recurrence of FSGS after kidney transplantation in adults. *Clin J Am Soc Nephrol*. 2020;15:247–256.
2. Canaud G, Zuber J, Sberro R, et al. Intensive and prolonged treatment of focal and segmental glomerulosclerosis recurrence in adult kidney transplant recipients: a pilot study. *Am J Transplant*. 2009;9:1081–1086.
3. Garrouste C, Canaud G, Buchler M, et al. Rituximab for recurrence of primary focal segmental glomerulosclerosis after kidney transplantation: clinical outcomes. *Transplantation*. 2017;101:649–656.
4. Hengel FE, Dehde S, Lasse M, et al. Autoantibodies targeting nephrin in podocytopathies. *N Engl J Med*. 2024;391:422–433.
5. Trachtman H, Laskowski J, Lee C, et al. Natural antibody and complement activation characterize patients with idiopathic nephrotic syndrome. *Am J Physiol Renal Physiol*. 2021;321:F505–F516.
6. Angeletti A, Bin S, Magnasco A, et al. Efficacy of combined rituximab and daratumumab treatment in posttransplant recurrent focal segmental glomerulosclerosis. *Am J Transplant*. 2024;24:688–692.
7. Randone P, Sanna E, Dolla C, et al. Rescue with obinutuzumab and daratumumab as combined B cell/plasma cell targeting approach in severe posttransplant focal segmental glomerulosclerosis recurrence. *Am J Transplant*. 2024;24:1896–1900.
8. Delbet JD, Hogan J, Parmentier C, et al. Successful global anti-B-cell strategy with daratumumab in a patient with post-transplant nephrotic syndrome recurrence unresponsive to immunoadsorption and obinutuzumab. *Pediatr Transplant*. 2023;27:e14544.
9. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100:S1–S276.
10. Liu P, Liu S, Dalal V, et al. Evaluation of methodologies in anti-nephrin autoantibody detection. *Kidney Int*. 2025;108:485–490.
11. Watts AJB, Keller KH, Lerner G, et al. Discovery of autoantibodies targeting nephrin in minimal change disease supports a novel autoimmune etiology. *J Am Soc Nephrol*. 2022;33:238–252.
12. Raglianti V, Angelotti ML, Cirillo L, et al. Anti-slit diaphragm antibodies on kidney biopsy identify pediatric patients with steroid-resistant nephrotic syndrome responsive to second-line immunosuppressants. *Kidney Int*. 2024;106:1124–1134.
13. Raglianti V, Angelotti ML, De Chiara L, et al. Anti-slit antibodies against podocin and kirrel1 in pediatric and adult podocytopathies. *J Am Soc Nephrol*. 2025;36:702–705.
14. Strassheim D, Renner B, Panzer S, et al. IgM contributes to glomerular injury in FSGS. *J Am Soc Nephrol*. 2013;24:393–406.
15. Panzer SE, Laskowski J, Renner B, et al. IgM exacerbates glomerular disease progression in complement-induced glomerulopathy. *Kidney Int*. 2015;88:528–537.
16. Angeletti A, Cantarelli C, Petrosyan A, et al. Loss of decay-accelerating factor triggers podocyte injury and glomerulosclerosis. *J Exp Med*. 2020;217:e20191699.
17. Angeletti A, Bin S, Kajana X, et al. Combined rituximab and daratumumab treatment in difficult-to-treat nephrotic syndrome cases. *Kidney Int Rep*. 2024;9:1892–1896.

18. Hengel FE, Dehde S, Yilmaz A, et al; PodoNet Consortium and the International Society of Glomerular Disease. Anti-nephrin autoantibodies in steroid-resistant nephrotic syndrome may inform treatment strategy. *Kidney Int*. 2025;107:1099–1103.
19. Hengel FE, Huber TB, Tomas NM. Potential and pitfalls of measuring circulating anti-nephrin autoantibodies in glomerular diseases. *Clin Kidney J*. 2025;18:sfaf100.
20. Bigatti C, Angeletti A, Kajana X, et al. Daratumumab efficacy in steroid-resistant nephrotic syndrome correlates with CD38+ B-cell depletion. *Kidney Int Rep*. 2025;10:3698–3700.
21. Lin Y, Pan Y, Han Q, et al. Obinutuzumab may be an effective and safe option for adult minimal change disease and focal segmental glomerulosclerosis patients after multitarget therapy including rituximab. *Am J Nephrol*. 2025;56:111–120.
22. Chan EY, Lin KY, Yap DY, et al. Obinutuzumab as a viable therapeutic strategy in rituximab-refractory childhood frequently relapsing, steroid-dependent nephrotic syndrome that relapsed during B-cell depletion. *Pediatr Nephrol*. 2025;40:711–714.
23. Angeletti A, Caridi G, Kajana X, et al. Obinutuzumab in rituximab-resistant podocytopathies, a single-center experience. *Kidney Int Rep*. 2025;10:2873–2874.
24. Morandi F, Airoldi I, Marimpietri D, et al. CD38, a receptor with multifunctional activities: from modulatory functions on regulatory cell subsets and extracellular vesicles, to a target for therapeutic strategies. *Cells*. 2019;8:1527.
25. van de Donk NWCJ, Usmani SZ. CD38 antibodies in multiple myeloma: mechanisms of action and modes of resistance. *Front Immunol*. 2018;9:2134.