American Journal of Transplantation 24 (2024) 688–692

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Case Report

Efficacy of combined rituximab and daratumumab treatment in posttransplant recurrent focal segmental glomerulosclerosis

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ARTICLE INFO

Keywords:
focal segmental glomerulosclerosis
kidney transplant
recurrence
rituximab
daratumumab

ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is one of the leading causes of kidney failure and it is characterized by a high rate of recurrence after kidney transplant. Moreover, FSGS recurrence is worsened by an increased risk of graft failure. Common therapies for FSGS recurrence mostly consist of plasma exchange treatments, also for prolonged time, and rituximab, with variable efficacy. We report 5 cases of early FSGS recurrence after kidney transplant, resistant to plasma exchange and rituximab treatment that subsequently resolved after combined therapy with rituximab and daratumumab. All cases were negative for genetic FSGS. The combined treatment induced a complete response in all the cases and was well tolerated. We also performed a comprehensive flow cytometry analysis in 2 subjects that may suggest a mechanistic link between plasma cells and disease activity. In conclusion, given the lack of viable treatments for recurrent FSGS, our reports support the rationale for a pilot trial testing the safety/efficacy profile of combined rituximab and daratumumab in posttransplant FSGS recurrence.

1. Introduction

Focal segmental glomerulosclerosis (FSGS), one of the leading causes of kidney failure in adults,[1] often recurs after kidney transplantation.[2] Plasma exchange (PEX) and the anti-CD20 monoclonal antibody rituximab represent the most common therapies for recurrent FSGS, but they are variably effective[3] and poorly tolerated, especially when PEX treatments are performed for a prolonged time.[4,5] As a result, FSGS recurrence leads to accelerated graft loss and its treatment represents a major unmet clinical need.[6]

Abbreviations: FSGS, focal segmental glomerulosclerosis; PEX, plasma exchange.

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https://doi.org/10.1016/j.ajt.2023.12.010
Received 27 August 2023; Received in revised form 15 November 2023; Accepted 1 December 2023
Available online 14 December 2023

Herein, we report 5 cases of early FSGS recurrence after kidney transplant, resistant to PEX and rituximab treatment that subsequently resolved after combined therapy with rituximab and daratumumab, a CD38-directed monoclonal depleting antibody.

2. Cases presentation

The Table reports the main baseline characteristics of the 5 patients with FSGS recurrence. All cases were negative for causative pathogenic gene variants for FSGS (Supplementary Methods).

Rituximab and daratumumab were administered as single doses at 375 mg/m^2 and 16 mg/kg, respectively. Details of treatment are provided in the Supplementary Appendix.

Patients 1 and 2 were 2 young females who presented with biopsy-proven recurrent FSGS and impaired graft function shortly after transplant (Supplementary Fig. 1). Due to unresponsiveness to PEX, combined rituximab and daratumumab treatment was initiated, based on the hypothesis that both CD20$^+$ B cells and CD38$^+$ long-lived plasma cells play a pathological role in FSGS (NCT05704400).[4] Combined treatment induced prompt proteinuria remission and significative improvement of kidney function (Fig.). At 4 months after treatment, patient 1 is still in remission without PEX. Patient 2 had a significant proteinuria reduction that allowed an initial reduction of PEX frequency from 3/week to 1 PEX every 15 days and then stop PEX treatment. After combined treatment, the 2 patients developed cytomegalovirus positivity with a prompt response to valganciclovir.

Patients 3 and 4 developed a biopsy-proven FSGS recurrence after the first year posttransplant (Table). Treatments with rituximab and chronic weekly PEX failed to induce full remission (Fig.). At the time of combined rituximab plus daratumumab treatment, both patients had nephrotic-range proteinuria, severe hypoalbuminemia, and normal renal graft function. Further kidney biopsies performed before combined treatment showed not-

Table
Main baseline characteristics at the time of combined treatment.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, sex, race	18 y, female, Caucasian	18 y, female, Caucasian	24 y, male, Caucasian	16 y, male, Caucasian	21 y, male, Caucasian
Time at FSGS recurrence after KT	23 d	3 d	11 d	18 d	21 d
Time of treatment after KT	5 wk	11 wk	3 y	2 y	7 y
Graft biopsy	Y	Y	Y	Y	Y
Donor specific antibodies	N	N	N	N	N
Proteinuria (g/24 h)	5	3.5	13	3.9	3.4
Serum Albumin (g/dL)	1.8	2.8	1.6	2.1	1.8
Serum creatinine (mg/dl)	2.1	1.4	0.8	0.5	1.7
eGFR[a] (mL/min/1.73m^2)	42	74	92	98	51
N' of previous rituximab doses	0	0	1	2	2
Months since last rituximab dose	N/A	N/A	11	9	51
PEX regimen	3/weekly	3/weekly	1/weekly	1/weekly	None
Induction treatment	Basiliximab	Basiliximab	Basiliximab	Basiliximab	Basiliximab
Immunosuppressive regimen[b]	Ste, FK, MMF	Ste, FK, MMF	Ste, FK, MMF	Ste, FK, MMF	Ste, FK, MMF
Age at FSGS onset in native kidneys	5 y	12 y	16 y	8 y	10 y
Native kidney biopsy	Y	Y	Y	Y	Y
Follow-up					
Follow-up after last infusion	4	7	12	12	10
Proteinuria (g/24 h)	0.4	0.5	0.6	0.3	0.9
Serum creatinine (mg/dL)	1.2	0.9	0.9	0.7	1.6
Serum albumin (g/dL)	3.9	3.5	3.9	3.8	3.4

CNI, calcineurin inhibitors; FK, tacrolimus; FSGS, focal segmental glomerulosclerosis; KT, kidney transplant; MMF, mycophenolate mofetil; PEX, plasma exchange; Ste, steroids.

[a] eGFR was calculated based on CKD-EPI formula.

[b] Target serum levels of FK: 8 to 10 ng/dL and 6 to 8 ng/dL for kidney transplant $<$ or $>$ 1 y, respectively; mycophenolate mofetil was given at the dose of 1 g, twice daily.

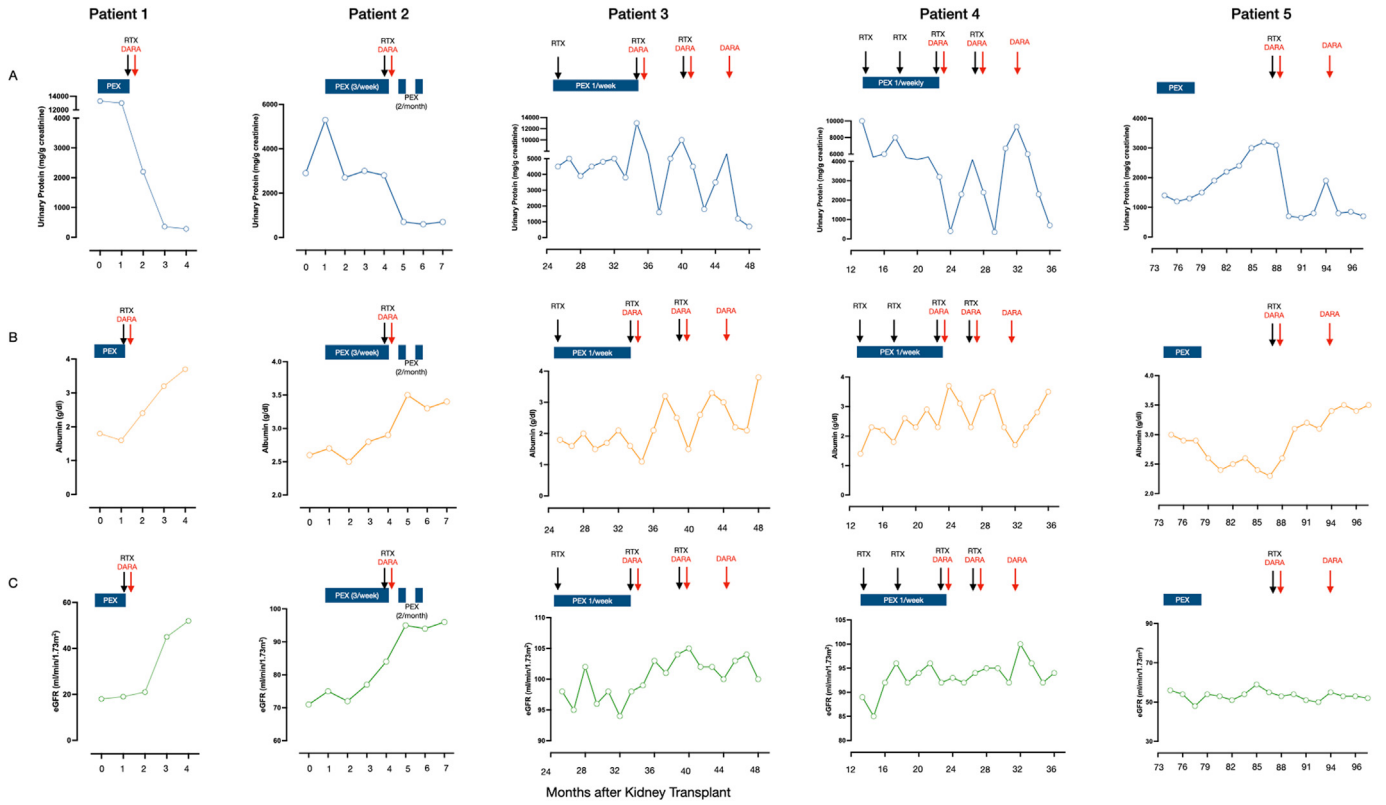

Figure. Clinical response to combined treatment with rituximab (RTX) and daratumumab (DARA). Panels show the course of proteinuria, measured as milligrams of urinary protein per gram of creatinine (A), serum albumin (g/dL) (B), and renal function (estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) (C). PEX, plasma exchanges.

otherwise-specified focal segmental lesions and focal adhesion between glomerulus stuff and Bowman's capsule in patients 3 and 4, respectively (Supplementary Fig. 1). Combined rituximab and daratumumab treatment induced prompt proteinuria remission and allowed for PEX interruption. In both patients, proteinuria relapsed at 4 months after treatment but responded to a second course of combined therapy. A second relapse was successfully treated with daratumumab alone (Fig.). At present, both patients are in full remission without PEX.

Patient 5 was a young male with biopsy-proven FSGS recurrence at 7 years posttransplant who achieved partial remission for 6 years through weekly PEX. When PEX treatment was stopped, the proteinuria relapsed in a few weeks. Combined rituximab and daratumumab treatment promptly reduced proteinuria, which relapsed at 4 months thereafter, but responded to a second dose of daratumumab alone. The patient is currently in remission without PEX (Fig.).

The protocol was approved by the IRCCS Giannina Gaslini Institute (Genoa, Italy) ethics committee, and all patients or relatives (in case of patients younger than 18 years), provided written informed consent before enrolment (CBUF-IGG2021).

In all patients, combined rituximab and daratumumab treatment was well tolerated. Minor or moderate respiratory symptoms occurred during 43% of daratumumab infusions, requiring slowing and/or temporary interruption of infusions. However, all infusions have been completed.

After combined treatment, all patients had low levels of circulating B cells, IgM, and IgG (Supplementary Fig. 2). In patients 1 and 3, we performed a comprehensive flow cytometry analysis of Peripheral Blood Mononuclear Cells (PBMCs) (Supplementary Appendix), comparing samples collected at enrolment and at 3 months after combined treatment. Circulating $CD38^{+}$ plasma cells at 3 months after daratumumab were still depleted in patient 1 with persistent remission, while they resulted at similar values in patient 3 with disease relapse (Supplementary Table 1), suggesting an early recovery or a lack of depletion after the combined treatment. Such findings may suggest a mechanistic link between plasma cells and disease activity.[7] Immune phenotyping did not reveal other major changes after treatment (Supplementary Table 2). Moreover, serum levels of anti-CD40 antibodies at 3 months after combined infusions did not correlate with the decrease of proteinuria (Supplementary Fig. 3). We did not perform kidney biopsies after combined treatment.

3. Discussion

To the best of our knowledge, this is the first report of the successful use of combined rituximab and daratumumab treatment in patients with FSGS recurrence after kidney transplant. Posttransplant FSGS recurrence is generally resistant to common treatments and cases that achieve PEX-depend remission are burdened by a high risk of infections and really poor quality of

life. Therefore, our findings respond to a major unmet clinical need and provide new hope for affected patients.

The pathogenic role of B cells in FSGS is supported by the cases in which B cell depletion reduces disease severity. However, the efficacy of rituximab in FSGS recurrence is limited.[6,8] Autoantibodies and plasma cells have been recently implicated in FSGS recurrence pathogenesis.[7,9] Unlike short-lived plasmablasts, long-lived plasma cells, a major source of antibodies, are unresponsive to anti-CD20 immunosuppressive treatments and highly express CD38. This formed the basis for our combined treatment with rituximab plus daratubumab.[10]

In a recent clinical study, the humanized anti-CD20 antibody obinutuzumab was combined with daratumumab to treat 14 subjects with treatment-resistant steroid-dependant/frequent-relapsing nephrotic syndrome,[11] a condition that is thought to share pathophysiological similarities with FSGS. The combined treatment induced longer remission than prior administration of rituximab alone.[12] However, similar to our experience, this study does not distinguish the roles of rituximab and daratumumab in promoting disease remission.

Our immune phenotypic analyses showing an association between the presence of CD38+ plasma cells in the circulating and disease activity suggest that daratumumab plays a critical therapeutic role. This is further supported by the fact that in our patients with disease relapse after the initial response to rituximab plus daratumumab, treatment with daratumumab alone was effective in promoting disease remission. Further mechanistic clinical studies will be important in defining the relative therapeutic role of rituximab versus daratumumab and understanding disease pathophysiology.

Overall, combined treatment was well tolerated. PEX interruption and disease remission significantly improved the quality of life in all the cases. Patients receiving combined treatment in the first months after kidney transplant (patient 1 and patient 2) developed CMV-DNA positivity, which was effectively treated with antiviral therapy. No other infections were reported.

Recently, Scalzo et al[13] described early severe T cell–mediated rejection in a kidney transplant recipient who received daratumumab prior to the kidney transplant as multiple myeloma therapy. The authors suggest that daratumumab promoted T cell expansion leading to acute rejection. However, previous experiences with daratumumab in kidney transplantation as a treatment for myeloma or as a desensitization drug,[14,15] did not describe an increased risk of T cell–mediated rejection. Therefore, our present data concur to support the safety of daratumumab infusion in kidney transplant recipients, but larger studies are needed to test this further.

In conclusion, given the lack of viable treatments for recurrent FSGS and the excellent safety profile of combined rituximab and daratumumab treatment, the present data support the rationale for a pilot trial testing the safety/efficacy profile of this strategy in posttransplant FSGS recurrence.

Acknowledgments

The authors thank Dr Elisa Buti (Meyer Children's Hospital, Florence, Italy), Dr Franco Sopranzi (Nephrology and Dialysis, General Hospital of Macerata, Macerata, Italy), and Dr Antonella Trivelli (IRCCS Istituto Giannina Gaslini, Genoa, Italy) for taking care of the reported patients.

Funding

Andrea Angeletti was supported with public funds granted by the Italian Ministry of Health "Ricerca Corrente."

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Data availability

The authors declare that all data supporting the findings of this study are available within the article and its Supplementary Material.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2023.12.010.

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