American Journal of Transplantation 24 (2024) 1896–1900

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Case Report

Rescue with obinutuzumab and daratumumab as combined B cell/plasma cell targeting approach in severe posttransplant focal segmental glomerulosclerosis recurrence

Paolo Randone [1,†], Enrico Sanna [1,†], Caterina Dolla [1], Ester Gallo [1], Silvia Mingozzi [1], Rita Tarragoni [1], Maria Cristina Torazza [1], Anna Niarchos [1], Alberto Mella [1], Ana Maria Manzione [1], Antonella Barreca [2], Ilaria Deambrosis [1], Roberta Giraudi [1], Luigi Biancone [1,*]

[1] *Renal Transplantation Center "A. Vercellone," Division of Nephrology Dialysis and Transplantation, Department of Medical Sciences, Città Della Salute e Della Scienza Hospital and University of Turin, Corso Bramante, Turin, Italy*
[2] *Pathology Unit, University of Turin, Città Della Salute e Della Scienza, Turin, Italy*

ARTICLE INFO

Keywords:
focal segmental
kidney transplant
obinutuzumab
daratumumab

ABSTRACT

The recurrence of primary focal segmental glomerulosclerosis (FSGS) after kidney transplantation is associated with a high graft loss rate with standard treatments based on plasmapheresis with/without rituximab. We present 2 consecutive cases of nongenetic early severe recurrent FSGS refractory to rituximab and anti–interleukin 1 treatment and with a partial response to plasmapheresis. Case 1 was a 22-year-old man who was rescue-treated for recurrence 36 weeks after transplantation with obinutuzumab (1000 mg/1.73 m^2, 1 dose) and daratumumab (18 mg/kg each dose, 8 doses), resulting in plasmapheresis discontinuation and a drop of proteinuria from 29 to 2.3 g/d. Proteinuria increased with circulating $CD38^+$ plasma cells and responded to an additional daratumumab dose. Currently, the proteinuria is 1.8 g/d, 14.5 months after discontinuing plasmapheresis and starting obinutuzumab and daratumumab therapy. Case 2 was a 15-year-old girl who was plasmapheresis dependent with 2 g/d proteinuria 82 weeks after transplantation, with a Tesio catheter in the right jugular vein as the only possible vascular access. After treatment

Abbreviations: eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IFTA, interstitial fibrosis, tubular atrophy; KB, kidney biopsy; KT, kidney transplant; mAb, monoclonal antibody; MMF, mycophenolate mofetil; NS, nephrotic syndrome; PEX, plasma exchange.

* Corresponding author. Pathology Unit, University of Turin, Città Della Salute e Della Scienza, Corso Dogliotti 14, Turin 10126, Italy.
E-mail address: luigi.biancone@unito.it (L. Biancone).
† These authors contributed equally: Paolo Randone and Enrico Sanna.

https://doi.org/10.1016/j.ajt.2024.06.010
Received 21 November 2023; Received in revised form 8 June 2024; Accepted 11 June 2024
Available online 17 July 2024

with obinutuzumab and daratumumab (1 dose each), she achieved stable complete remission (0.3 g/d proteinuria) with persistent plasmapheresis discontinuation. These cases suggest the potential of combining obinutuzumab with daratumumab for the treatment of recurrent FSGS.

1. Introduction

Recurrence of primary focal segmental glomerulosclerosis (FSGS) after kidney transplant (KT) occurs in approximately one-third of patients, with FSGS being the underlying cause of native kidney disease. Only a minority of these patients achieve complete remission with the current standard treatment of plasmapheresis, with or without rituximab, a type I anti-CD20 monoclonal antibody (mAb) targeting B cells.[1]

Recently, the association of obinutuzumab, a humanized type II anti-CD20 mAb with superior B cell-depletion activity, and daratumumab, a plasma cell–depleting anti-CD38 humanized mAb, has shown efficacy in some cases of nonbiopsied steroid-dependent nephrotic syndrome (NS).[2,3]

Herein, we present 2 consecutive cases of fully characterized early severe recurrent FSGS refractory to rituximab, scarcely (case 1) or partially (case 2) responsive to an interleukin (IL)-1 blocker receptor antagonist (anakinra) and plasma exchange (PEX) with subsequent dependency, which successfully responded to combined obinutuzumab and daratumumab treatment.

2. Case 1

A 16-year-old Caucasian boy presented with hypertension and NS in 2017 (Table). A kidney biopsy (KB) revealed minimal change disease. The patient was initially treated with steroids and calcineurin inhibitors, followed by 2 doses of rituximab without a response. A genetic study found heterozygous nucleotide variants without a documented pathogenic role in *LAMA 5* gene (Supplementary Table S1). After 2 years, the patient experienced rapid deterioration of kidney function with massive proteinuria. The second KB revealed FSGS, collapsing variant. PEX was unsuccessful, and hemodialysis was initiated. In March 2022, the patient received a KT from a deceased donor (Fig. 1A). Induction therapy included thymoglobulin, rituximab, and methylprednisolone, followed by tacrolimus, mycophenolate mofetil (MMF), and prednisone (Fig. 1). NS recurred 3 days posttransplant. Considering the disease's aggressiveness on native and transplant kidneys, we promptly started a combined treatment with PEX and anakinra, an IL-1 receptor antagonist previously associated with a positive response in 3 NS cases, including only 1 with FSGS recurrence.[4] This was based on favorable results obtained by uncoupling IL-1β/IL-1R1 in preventing the development of FSGS in a mouse model.[5] Stable kidney function (estimated glomerular filtration rate [eGFR]: 46 mL/min/1.73 m^2) was achieved; however, proteinuria remained high (10 g/d). KB revealed extensive podocyte effacement on electron microscopy involving about 88% to 90% of the capillary surface area (Fig. 2A, B), with associated podocyte microvillous transformation (Fig. 2C).

Intensive PEX 3 times in a week was barely able to prevent the need for dialysis, which was required on 3 occasions (weeks 10, 20, and 38) because of oligoanuria with fluid overload caused by a severe increase in proteinuria. During week 10, a second KB revealed acute tubular necrosis and negative C4d with persistent extensive podocyte effacement. Anakinra was discontinued around week 18 owing to infectious complications (acute cholecystitis and oral infection).

Three months later, the proteinuria increased (29 g/d), with a stable eGFR. We decided to start rescue therapy with obinutuzumab, followed by multiple doses of daratumumab until proteinuria was in partial remission without significant rebound. PEX was discontinued before obinutuzumab administration. During daratumumab administration, the patient experienced numerous adverse events including mild bronchospasm, hypertension, severe leukopenia, thrombocytopenia, hypogammaglobulinemia, and gingival and anal ulcers requiring antibiotics.

Following a new decline in eGFR, a third KB was performed (week 40), which showed mild interstitial fibrosis and tubular atrophy, isometric tubular cell vacuolization, and negative C4d in addition to FSGS. To minimize the tacrolimus trough level (approximately 2-3 ng/mL), conversion to belatacept and discontinuation of MMF was done. At week 78, after a new proteinuria relapse, rare circulating $CD38^+$ plasma cells were found, and an additional dose of daratumumab was administered, with subsequent depletion and clinical response (Supplementary Table S2). At week 94, eGFR was satisfactory with proteinuria at approximately 1.8 g/d without angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, 14.5 months after obinutuzumab administration.

3. Case 2

A 10-year-old Caucasian girl developed NS in 2017 with FSGS (not otherwise specified variant) on KB and negative genetic screening (Table). Subsequent tacrolimus and MMF treatment did not improve the symptoms. In 2020, unsuccessful attempts to create an arteriovenous fistula led to hemodialysis using the right jugular vein with Tesio catheter as the only possible vascular access. Two years later, she underwent living-donor KT (Fig. 1B). Induction therapy included thymoglobulin and methylprednisolone, followed by tacrolimus, MMF, and prednisone (Fig. 2). After 5 days, kidney function deteriorated, and proteinuria increased (17 g/d), suggesting FSGS recurrence, which was later confirmed by KB (Fig. 2D-F). PEX was initiated with rituximab and anakinra, leading to partial kidney function

Table
Main clinical characteristics of the two patients with FSGS recurrence.

Characteristic	Case 1	Case 2
Sex	Male	Female
Age at the diagnosis (y)	17	10
Native KB	I biopsy: MCD II biopsy: FSGS-collapsing variant	FSGS-NOS variant
Cumulative immunosuppressive treatment before transplant	ST/CYA/TAC/PEX/RTX	ST/MMF/TAC
Age at the start of dialysis treatment (y)	19	12
Type of dialysis	Hemodialysis	Hemodialysis
Type of vascular access for dialysis	Arteriovenous fistula	Long-Term catheter (Tesio)[a]
Age at transplant (y)	21	14
Type of transplant	Deceased donor	Living donor
Mismatch HLA (HLA-A/B/DR)	4/6	6/6
Graft biopsy	I Biopsy: FSGS, II Biopsy: ATN, III Biopsy: FSGS-NOS variant, CNI toxicity	FSGS-NOS variant
C4d on graft biopsy (every time)	Negative	Negative
Anti-HLA donor-specific antibodies	Negative	Negative

ATN, acute tubular necrosis; CNI, calcineurin inhibitor; CYA, cyclosporine A; FSGS, focal segmental glomerulosclerosis; KB, kidney biopsy; MCD, minimal change disease; MMF, mycophenolate mofetil; NOS, not otherwise specified; PEX, plasmapheresis; RTX, rituximab; ST, steroid; TAC, tacrolimus.

[a] Last available vascular access for dialysis maintenance in a patient with repeated access failure.

improvement but with high proteinuria (16 g/d). Owing to nonadherence to daily injections, anakinra was discontinued after 7 months. PEX frequency was reduced with kidney function stabilization but with PEX-dependent persistent proteinuria (2 g/d) without antiproteinuric agents.

Twenty-one months posttransplant, a partial response to PEX, the risk of Tesio infections, and her desire for Tesio removal led us to opt for a rescue-treatment with 1 dose each of obinutuzumab and daratumumab. Prompt treatment led to complete remission; therefore, PEX was discontinued. Five months after daratumumab treatment, the patient experienced mild leukopenia that responded to granulocyte colony–stimulating factor

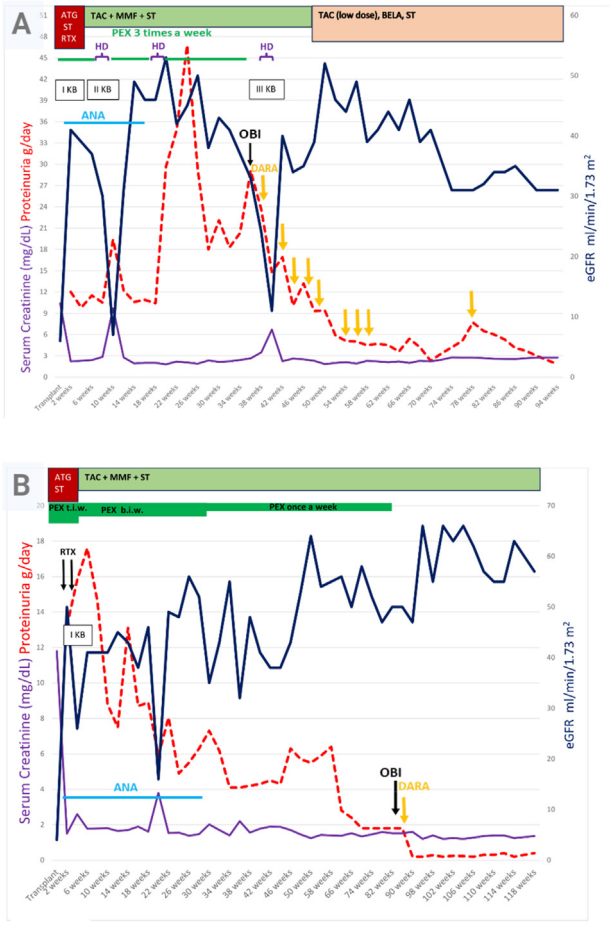

Figure 1. Timelines of events from the kidney transplant in cases 1 (A) and 2 (B). (A) Proteinuria was higher than 10 g/day until the start of rescue therapy with obinutuzumab and daratumumab. (B) Multiple immunosuppressive therapies were started after the recurrence of focal segmental glomerulosclerosis; however, only partial remission was achieved by weekly plasmapheresis. After the rescue therapy with obinutuzumab and daratumumab, complete remission was achieved, and the patient became plasmapheresis independent. ANA, anakinra; ATG, thymoglobulin; BELA, belatacept; b.i.w., bis in a week; DARA, daratumumab; HD, hemodialysis; MMF, mycophenolate mofetil; OBI, obinutuzumab; PEX, plasmapheresis; RTX, rituximab; ST, steroids; TAC, tacrolimus; t.i.w., 3 times a week.

administration and transient suspension of MMF. Currently, proteinuria is 0.3 g/d, with therapy based on tacrolimus, MMF, and prednisone without circulating $CD38^{+}$ plasma cells (Supplementary Table S2).

4. Discussion

To the best of our knowledge, these are the first 2 cases of well-characterized posttransplant FSGS recurrence rescued with obinutuzumab and daratumumab. Conventional therapy was insufficient to achieve remission in both patients. Limited evidence exists supporting the use of anakinra for the treatment of FSGS recurrence after transplantation, given that this is an experimental treatment. Angeletti et al[4,5] recently identified a role of IL-1β/IL-1R1 in promoting the disease, showing the benefit of

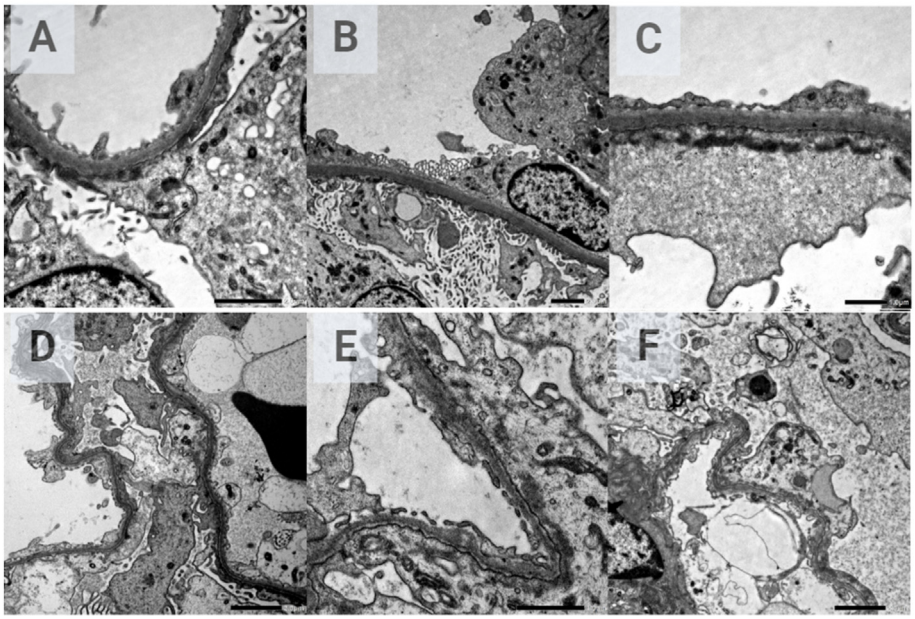

Figure 2. Representative images of kidney biopsies in cases 1 and 2. Electron microscopy (A-F): In case 1, first graft biopsy shows extensive podocyte foot process effacement, involving about 88% to 90% of capillary surface area (A, original magnification: ×5000; B, original magnification: ×4000), assessed in the nonsclerosed glomerulus, with associated podocyte microvillous transformation (C, original magnification: ×2000). In case 2, widespread foot process effacement is observed in approximately 93% of the capillary surface area of the nonsclerosed glomerulus (D-F, original magnification: ×3000).

anakinra addition to PEX and rituximab in a patient with FSGS recurrence. Conceivably, the IL-1 blockade might have partially influenced the disease behavior in our patients; however, a clear improvement in the outcome was obtained only after combined therapy with obinutuzumab and daratumumab in both patients.

Recently, Angeletti et al[6] combined rituximab and daratumumab to treat recurrent FSGS after KT in 5 patients. Only 2 patients (cases 3 and 4 of that article) who were resistant to PEX and rituximab experienced nephrotic proteinuria recurrences every 4 to 6 weeks after daratumumab doses. Furthermore, all patients received a lower immunosuppressive induction with basiliximab. Therefore, second-generation anti-CD20 mAb therapy with stronger activity than that of rituximab could be a better solution.[2,7]

Regarding the daratumumab protocol in our cases, multiple doses of daratumumab in case 1 were used until proteinuria was in partial remission without significant rebounds, whereas a single dose was given in case 2 because proteinuria quickly decreased and maintained the response without subsequent rebounds.

Refractory cases may hypothetically depend on the limited depletion of memory B cells[8] and/or plasma cells,[6] which was confirmed by our experience where prolonged depletion and response was observed in case 2, whereas there was a relapse with $CD38^{+}$ circulating plasma cells and a prompt response to an additional daratumumab dose in case 1.

Leukopenia and infectious complications were mainly observed during the daratumumab cycles. Conceivably, the susceptibility to infections in refractory patients may be proportional to the stratification of lines of previous unsuccessful immunosuppressive treatments.

In conclusion, these data warrant further investigation of B cell and plasma cell depletion in managing posttransplant FSGS recurrence that fails to respond to conventional therapy with PEX with or without rituximab.

Acknowledgments

The authors thank Drs M. Scaldaferri and F. Cattel (Pharmaceutical Committee, Città della Salute e della Scienza di Torino, University Hospital); Dr B. Gianoglio and Dr L. Peruzzi (Pediatric Nephrology Unit, Regina Margherita Children's Hospital, Turin); Nadia Martinetti (Pathology Unit, University of Turin, Città Della Salute e Della Scienza); Marta Gai (Open Lab of Advanced Microscopy—OLMA—at the Molecular Biotechnology Center); and Lucia Massari (Renal Immunopathology Laboratory, Division of Nephrology Dialysis and Transplantation, Department of Medical Sciences, Città Della Salute e Della Scienza Hospital and University of Turin) for their expert support.

Funding

The study was funded by the "TGT study" (University of Turin, Department of Medical Sciences) and "CRT Foundation" grants to LB and by the PRIN 2022 grant code 2022LTXXRP (Italian Ministry of University and Research) to AM.

Declaration of competing interests

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

Data availability

All data generated or analyzed during this study are included in this article and in the supplementary material. Further inquiries can be directed to the corresponding authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2024.06.010.

ORCiD

Paolo Randone https://orcid.org/0009-0000-6388-2109
Enrico Sanna https://orcid.org/0009-0009-4995-348X
Caterina Dolla https://orcid.org/0000-0002-2981-699X
Ester Gallo https://orcid.org/0000-0001-5105-4947
Silvia Mingozzi https://orcid.org/0000-0002-0772-9393
Rita Tarragoni https://orcid.org/0000-0002-2685-4384
Maria Cristina Torazza https://orcid.org/0009-0009-2938-9826
Anna Niarchos https://orcid.org/0009-0003-8504-9101
Alberto Mella https://orcid.org/0000-0001-6387-5005
Ana Maria Manzione https://orcid.org/0000-0003-2620-491X
Antonella Barreca https://orcid.org/0000-0003-3566-1995
Ilaria Deambrosis https://orcid.org/0000-0002-2677-9310
Roberta Giraudi https://orcid.org/0009-0005-6104-508X
Luigi Biancone https://orcid.org/0000-0002-7700-6350

References

1. Uffing A, Pérez-Sáez MJ, Mazzali M, et al. Recurrence of FSGS after kidney transplantation in adults. *Clin J Am Soc Nephrol*. 2020;15(2):247–256. https://doi.org/10.2215/CJN.08970719.
2. Delbet J-D, Hogan J, Parmentier C, Ulinski T, Dossier C. 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(5):e14544. https://doi.org/10.1111/petr.14544.
3. Majeranowski A, Okrój M. Regarding: a global anti-B cell strategy combining obinutuzumab and daratumumab in severe pediatric nephrotic syndrome. *Pediatr Nephrol*. 2021;36(6):1651–1652. https://doi.org/10.1007/s00467-021-04981-5.
4. Angeletti A, Magnasco A, Antonella Trivelli, et al. Refractory minimal change disease and focal segmental glomerular sclerosis treated with anakinra. *Kidney Int Rep*. 2022;7(1):121–124. https://doi.org/10.1016/j.ekir.2021.10.018.
5. Angeletti A, Cantarelli C, Petrosyan A, et al. Loss of decay-accelerating factor triggers podocyte injury and glomerulosclerosis. *J Exp Med*. 2020;217(9):e20191699. https://doi.org/10.1084/JEM.20191699.
6. Angeletti A, Bin S, Magnasco A, Bruschi M, Cravedi P, Ghiggeri GM. Efficacy of combined rituximab and daratumumab treatment in posttransplant recurrent focal segmental glomerulosclerosis. *Am J Transplant*. 2024;24(4):688–692. https://doi.org/10.1016/j.ajt.2023.12.010.
7. Dossier C, Hogan J. Reply to Angeletti et al-efficacy of combined rituximab and daratumumab treatment in posttransplant recurrent focal segmental glomerulosclerosis. *Am J Transplant*. 2024;24(7):1325–1326. https://doi.org/10.1016/j.ajt.2024.02.016.
8. Ramos EJ, Pollinger HS, Stegall MD, Gloor JM, Dogan A, Grande JP. The effect of desensitization protocols on human splenic B-cell populations in vivo. *Am J Transplant*. 2007;7(2):402–407. https://doi.org/10.1111/j.1600-6143.2006.01632.x.