Kidney Medicine

Early Experience With Iptacopan for Recurrent IgA Nephropathy After Kidney Transplantation

Ayman Al Jurdi, Abraham Cohen Bucay, Pitchaphon Nissaisorakarn, Hannah Gilligan, Claire T. Avillach, Veronica E. Klepeis, Rex N. Smith, Ragnar Palsson, Kassem Safa, and Leonardo V. Riella

Immunoglobulin A (IgA) nephropathy is a common cause of kidney failure and can recur after kidney transplantation, increasing the risk of allograft loss. Effective treatments for recurrent IgA nephropathy in kidney transplant recipients are urgently needed. Iptacopan is a complement factor B inhibitor that received accelerated approval by the US Food and Drug Administration in August 2024 for the treatment of high-risk native IgA nephropathy based on trials that excluded transplant recipients. In this case series, we report our early experience with iptacopan in three individuals with biopsy-confirmed recurrent IgA nephropathy after kidney transplant. All received iptacopan for ≥3 months in combination with a short course of systemic corticosteroids. Two individuals demonstrated significant reductions in proteinuria and resolution of microscopic hematuria. One individual developed progressive graft dysfunction; repeat biopsy showed persistent active glomerulonephritis with codeposition of IgG, suggesting a more aggressive or atypical disease phenotype. These early data suggest that iptacopan, in combination with short-term corticosteroids, may offer therapeutic benefit in selected kidney transplant recipients with recurrent IgA nephropathy, warranting further investigation.

Complete author and article information provided before references.

Correspondence to A. Al Jurdi (aaljurdi@mgh.harvard.edu)

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IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and frequently progresses to kidney failure.[1,2] Kidney transplantation is the optimal treatment for kidney failure. IgAN can recur in the allograft with an estimated cumulative incidence of 23% at 15 years.[3] Posttransplant recurrence of IgAN is associated with a higher risk of allograft loss, particularly in those with proteinuria.[3] Therefore, effective treatments for recurrent IgAN are urgently needed. Iptacopan, a complement factor B inhibitor, recently received accelerated approval from the US Food and Drug Administration for the treatment of IgAN. This was based on the phase III Applause-IgAN trial, which showed a 38.3% in adjusted geometric mean 24-hour urine protein-creatinine ratio (UPCR) at 9 months.[4] However, the trial excluded kidney transplant recipients (KTRs), and its findings cannot be extrapolated to KTRs with recurrent IgAN. This is the first report of iptacopan use for recurrent IgAN in 3 KTRs.

CASE REPORT

The first individual is a 25-year-old woman with IgAN for which she never received treatment as she presented with kidney failure. She started dialysis then received a living donor kidney transplant from her father 4 years prior. She received basiliximab induction and maintenance immunosuppression with tacrolimus, 5 mg prednisone, and 180 mg mycophenolic acid twice daily because of prior BK viremia. She had a kidney allograft biopsy 3.5 years posttransplant for persistent microscopic hematuria and rising proteinuria (UPCR 0.53 g/g, urinary albumin-creatinine ratio [UACR] 0.31 g/g) despite supportive therapy with 100 mg losartan and 25 mg spironolactone. Her kidney function was at baseline with a serum creatinine of 1.1-1.3 mg/dL. She could not tolerate dapagliflozin because of recurrent urinary tract infections. The biopsy showed recurrent IgAN with mesangial hypercellularity and 10% fibrous/fibrocellular crescents (Oxford classification M1E0S1T1-C1) (Table 1). It also showed severe vascular disease and moderate chronic changes (43% global glomerulosclerosis [GG] and 25%-35% interstitial fibrosis/tubular atrophy [IFTA]). Immunofluorescence showed segmental granular mesangial staining for IgA (4+), IgG (segmental trace-1+), IgM (segmental trace), C3 (4+), kappa (segmental 2-3+), and lambda (segmental 2-3+), whereas C1q and fibrin were negative. Electron microscopy showed moderate foot process effacement (FPE) and mesangial electron-dense deposits (EDDs). She was switched from tacrolimus to belatacept given the severe vascular disease on biopsy.

Four months later, she was admitted to the hospital for a urinary tract infection complicated by acute kidney injury with a creatinine level of 4 mg/dL thought to be due to acute tubular injury. Her proteinuria also continued to increase (UPCR 1.8 g/g, UACR 1.3 g/g). She had a repeat biopsy during her admission (Fig 1A-E), which showed ongoing active IgAN with endocapillary hypercellularity, 10% cellular crescents, numerous red blood cell casts, and moderate acute tubular injury (M1E1S0T0-C1). The chronicity appeared less on this biopsy (5% GG and 5%-10% IFTA), likely because of differences in sampling. Electron microscopy showed moderate FPE, reactive swollen endothelium, and EDDs in the subendothelial and mesangial areas. Immunofluorescence showed global

Table 1. Summary of Cases of Recurrent IgA Nephropathy After Kidney Transplant

Case #	1	2	3
Age and sex	25, female	67, male	39, male
Transplant type	Living donor	Deceased donor	Deceased donor
Timing of biopsy that prompted treatment	46 months	86 months	12 months
MEST-C score	M1E1S0T0-C1	M1E1S0T0-C1	M1E1S0T0-C1
Immunofluorescence	IgA (2-3+), IgG (neg), IgM (neg), C3 (2-3+), C1q (neg)	IgA (3+), IgG (neg), IgM (neg), C3 (1+), C1q (trace)	IgA (4+), IgG (3+), IgM (trace), C3 (3+), C1q (neg)
Serum creatinine level at the time of biopsy (mg/dL)	1.1-1.3	3.4	1.4-1.7
UPCR/UACR at the time of biopsy (g/g)	1.8/1.3	3.3/2.1	2.7/1.7
Treatment	Steroids ×3 weeks Iptacopan (ongoing)	Steroids ×9 weeks Iptacopan (ongoing)	Steroids ×4 weeks Iptacopan (ongoing)
Duration of follow-up after iptacopan initiation	Four months	Three months	Four months
Serum creatinine level after treatment (mg/dL)	1.2	1.2	3.6
UPCR/UACR after treatment (g/g)	0.32/0.20	0.59/0.39	0.8-3.8/0.7-2.7
Response summary	Good response	Good response	No response

diffuse mesangial deposits that stained for IgA (2-3+, coarse granular), C3 (2-3+), kappa (1+), and lambda (1-2+) but were negative for IgM, IgG, and C1q. Given ongoing proteinuria, microscopic hematuria and disease activity on biopsy, the decision was made to treat with immunosuppressive therapy. After completion of her antibiotic course, she was started on 200 mg iptacopan twice daily and a 3-week course of prednisone (40 mg for 1 week, 20 mg for 1 week, and 10 mg for 1 week followed by return to maintenance 5 mg dose). The prednisone was used given the degree of disease activity on biopsy. Iptacopan was chosen given it is the only approved steroid-free immunosuppressive maintenance option for IgAN. She received MenB and MenACWY vaccines and remains on penicillin prophylaxis. After four months on iptacopan therapy, her proteinuria has decreased significantly (UPCR 0.32 g/g [82% reduction], UACR 0.20 g/g), her microscopic hematuria has improved (3+ to 1+) and her serum creatinine level remains stable at 1.2 mg/dL (Fig 1F-H). She continues on iptacopan therapy as well as belatacept, mycophenolic acid, and prednisone.

The second individual is 67-year-old man with kidney failure because of biopsy-proven diabetic kidney disease and crescentic IgAN. He was on hemodialysis for 6 years after which he received a deceased donor kidney transplant. He received antithymocyte globulin induction and maintenance immunosuppression with tacrolimus (trough levels 5-8 ng/mL), 500 mg mycophenolate mofetil twice daily, and 5 mg prednisone daily. Seven years after transplant, he presented with palpable petechial rash on his hands, feet, and buttocks and rapidly progressive glomerulonephritis (serum creatinine 1.1 to 3.4 mg/dL over 2 months, new microscopic hematuria, and new proteinuria UPCR 3.3 g/g, UACR 2.1 g/g) with severe hypertension (systolic blood pressure >200 mm Hg) for which he was admitted to the hospital. Intravenous methylprednisolone (500 mg × 3 days) was started while awaiting work-up results.

Serologic evaluation showed normal complement levels, normal monoclonal studies (serum free light chain K/L ratio 1.82, normal serum protein electrophoresis/urine protein electrophoresis), and normal autoimmune work-up (antinuclear antibody, double-stranded DNA, rheumatoid factor, cyoglobulins, anti-PLA2R, anti-neutrophil cytoplasmic antibody, and anti-GBM antibody). Skin biopsy of the left dorsal wrist showed leukocytoclastic vasculitis with 1+ IgA and 1-2+ C3 deposition, consistent with IgA vasculitis. Kidney allograft biopsy (Fig 2A-F) showed recurrent crescentic IgAN (M1E1S0T0-C1), severe acute tubular injury, and mild-moderate chronic changes (20% GG, 20% IFTA). Immunofluorescence showed IgA (3+, coarse granular), C3 (1+), C1q (trace), kappa (2+), lambda (1+), and negative IgM/IgG. Electron microscopy showed diffuse FPE and EDDs in the mesangial and subendothelial spaces.

His rash and kidney function began improving with intravenous steroids, as such oral steroids were administered and tapered over nine weeks (Fig 2G-I). Lisinopril (30 mg) was switched to 100 mg losartan. After completing his first round of meningococcal vaccinations and initiating penicillin VK prophylaxis, 200 mg oral iptacopan twice daily was initiated as maintenance therapy for IgA nephropathy. Given the severity of the kidney injury and the disease activity on biopsy, the decision was made that he would benefit from long-term immunosuppressive therapy for IgAN. Iptacopan was chosen given it is the only approved steroid-free immunosuppressive maintenance option for IgAN, even though it has not been studied in IgA vasculitis.

After 3 months on iptacopan therapy, his serum creatinine is 1.2 mg/dL, his proteinuria improved (UPCR

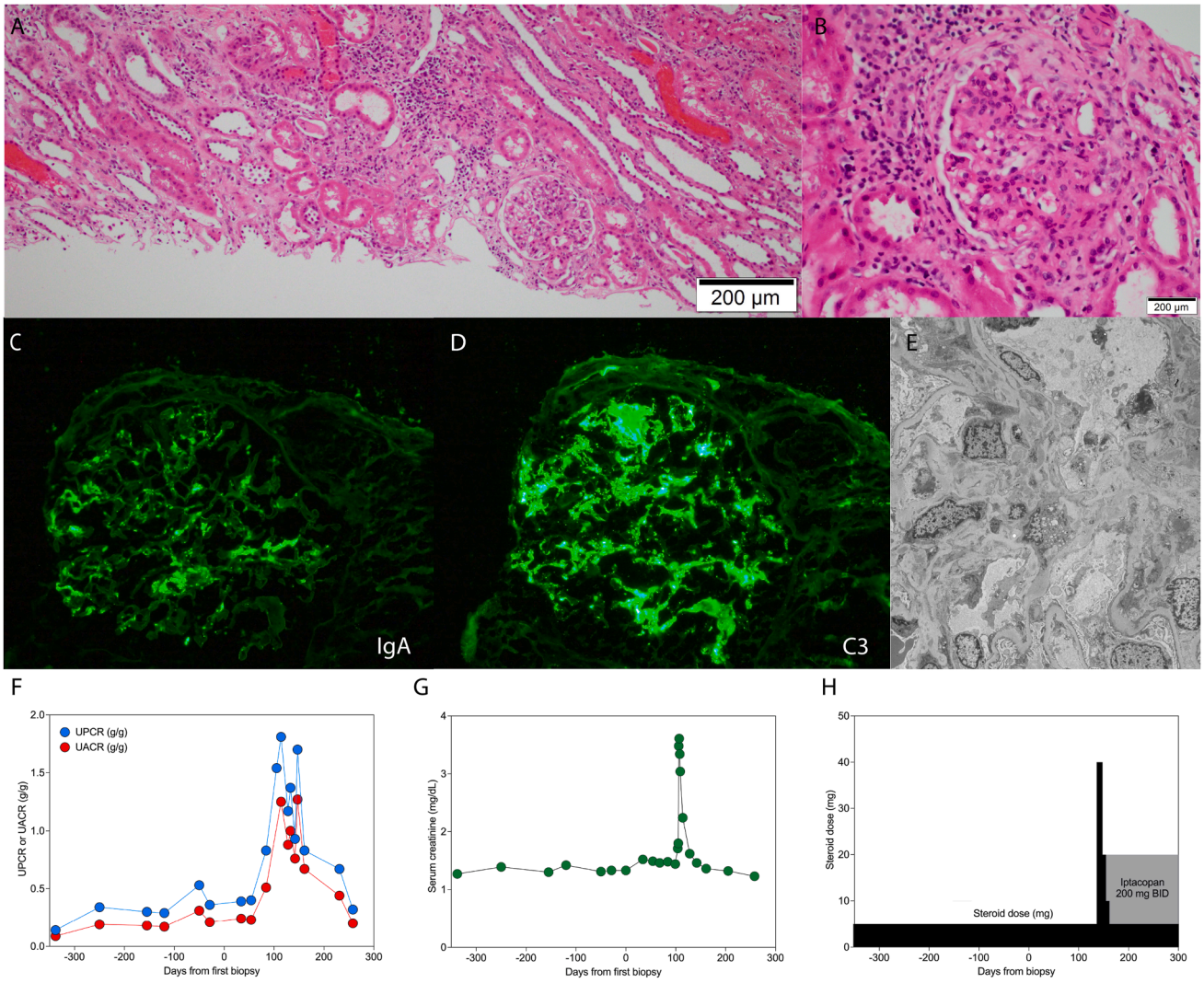

Figure 1. First case of recurrent IgA nephropathy. (A) Light microscopy showed ongoing active IgAN with endocapillary hypercellularity, 10% cellular crescents, numerous red blood cell casts and moderate acute tubular injury (10×, H&E stain) and (B) (40×, H&E stain). (C) Immunofluorescence showed global diffuse mesangial deposits that stained for IgA (2-3+) and (D) C_3 (2-3+). (E) Electron microscopy showed moderate foot process effacement, reactive swollen endothelium, and electron-dense deposits in the subendothelial and mesangial areas. (F) Clinical course with trends of urine protein-creatinine ratio (UPCR, blue circles), urine albumin-creatinine ratio (UACR, red circles), (G) serum creatinine (green circles), and (H) treatment regimen. Abbreviations: EDDs, electron-dense deposits; FPE, foot process effacement; H&E, hematoxylin and eosin; IgAN, IgA nephropathy.

0.59 g/g [82%], UACR 0.39 g/g), and his microscopic hematuria improved (from 3+ to trace-1+). There were no changes to supportive therapy during that time. He continues on iptacopan therapy as well as tacrolimus, mycophenolate mofetil, and prednisone (Table 1).

The third individual is a 39-year-old man with kidney failure attributed to IgAN. His native kidney disease presented with an elevated serum creatinine (1.5 mg/dL), microscopic hematuria, and nephrotic-range proteinuria (UPCR 9 g/g). Kidney biopsy at that time showed a membranoproliferative pattern of glomerular injury. Immunofluorescence showed fine granular reactivity for IgA (4+), IgG (3-4+), IgM (trace), C3 (3+), kappa LC (4+), lambda LC (1-2+), and fibrinogen (3+) both along the capillaries and in the mesangium. Electron microscopy (EM) showed moderate FPE and frequent mesangial and subendothelial EDDs, but no tubuloreticular inclusions. He was treated with systemic steroids with improvement in proteinuria to 1 g/g and stable creatinine. He had a relapse a few months later with increasing proteinuria (7 g/g) and serum creatinine levels that increased over the next year (1.5 to 2.8 mg/dL) despite treatment with 1,000 mg mycophenolate mofetil twice daily. He was switched to tacrolimus for 2 months but had persistent proteinuria (5 g/g) and increasing serum creatinine levels (3.6 to 5.1 mg/dL), so tacrolimus was withdrawn. As a last resort, he

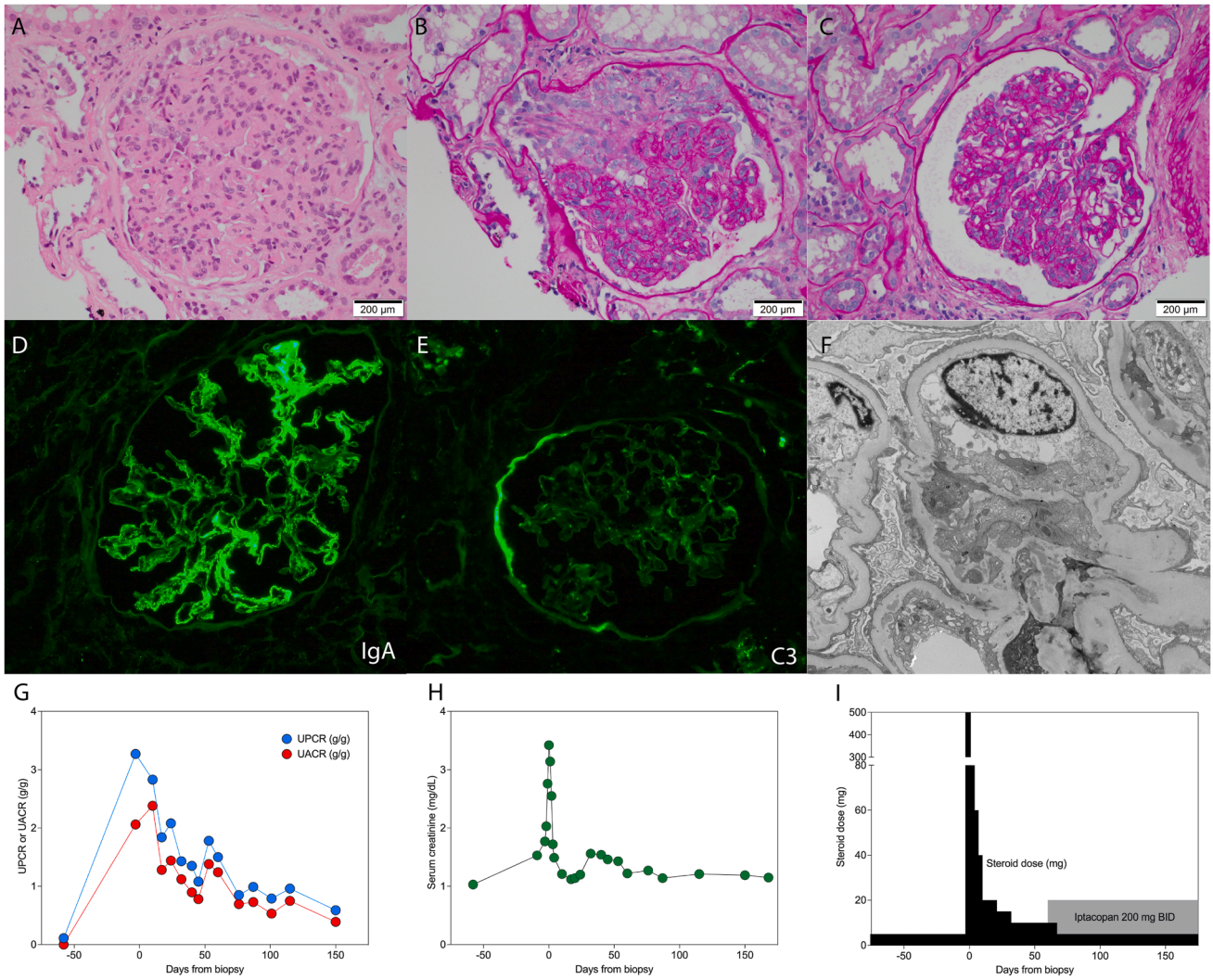

Figure 2. Second case of recurrent IgA nephropathy. (A) Light microscopy showed recurrent crescentic IgAN with mesangial and endocapillary hypercellularity, severe acute tubular injury, and mild-moderate chronic changes (40×, H&E stain) and (B, C) (40×, PAS stain). (D) Immunofluorescence showed coarse granular staining for IgA (3+) and (E) C_3 (1+). (F) Electron microscopy showed diffuse foot process effacement and electron-dense deposits in the subendothelial and mesangial spaces. (G) Clinical course with trends of urine protein-creatinine ratio (UPCR, blue circles), urine albumin-creatinine ratio (UACR, red circles), (H) serum creatinine (green circles), and (I) treatment regimen. Abbreviations: EDDs, electron-dense deposits; FPE, foot process effacement; H&E, hematoxylin and eosin; IF, immunofluorescence; IgAN, IgA nephropathy; PAS, periodic acid–Schiff.

then received another course of steroids, oral cyclophosphamide (cumulative dose 1.5 g), and rituximab (two doses of 1 g 2 weeks apart). He did not respond and initiated dialysis shortly after.

After 5 years receiving dialysis, he received a deceased donor kidney transplant with antithymocyte globulin induction. Maintenance immunosuppression consisted of tacrolimus (trough levels 7-9 ng/mL), 500 mg mycophenolate mofetil twice daily, and 5 mg prednisone daily. One year after transplant, he developed increasing proteinuria (UPCR 2.7 g/g, UACR 1.7 g/g) with microscopic hematuria, but his kidney function remained at baseline (serum creatinine 1.4-1.7 mg/dL). Of note, he reported intermittent cocaine use around this time, but his antineutrophil cytoplasmic antibody results were negative.

Kidney allograft biopsy showed crescentic IgAN with collapsing features (Fig 3A-F, M1E1S1T0-C1). There was 0% GG and less than 5% IFTA. Immunofluorescence showed granular mesangial staining for IgA (4+), IgG (3+ segmental), IgM (trace segmental), C3 (3+), kappa (2+ segmental), lambda (1+ segmental), and negative C1q. EM showed moderate FPE, mesangial EDDs, and tubuloreticular inclusions. He was admitted for expedited treatment. Intravenous methylprednisolone (500 mg) was administered and followed by a 4-week oral prednisone taper. After discharge, 200 mg iptacopan twice daily was initiated. Iptacopan was chosen given it is the only

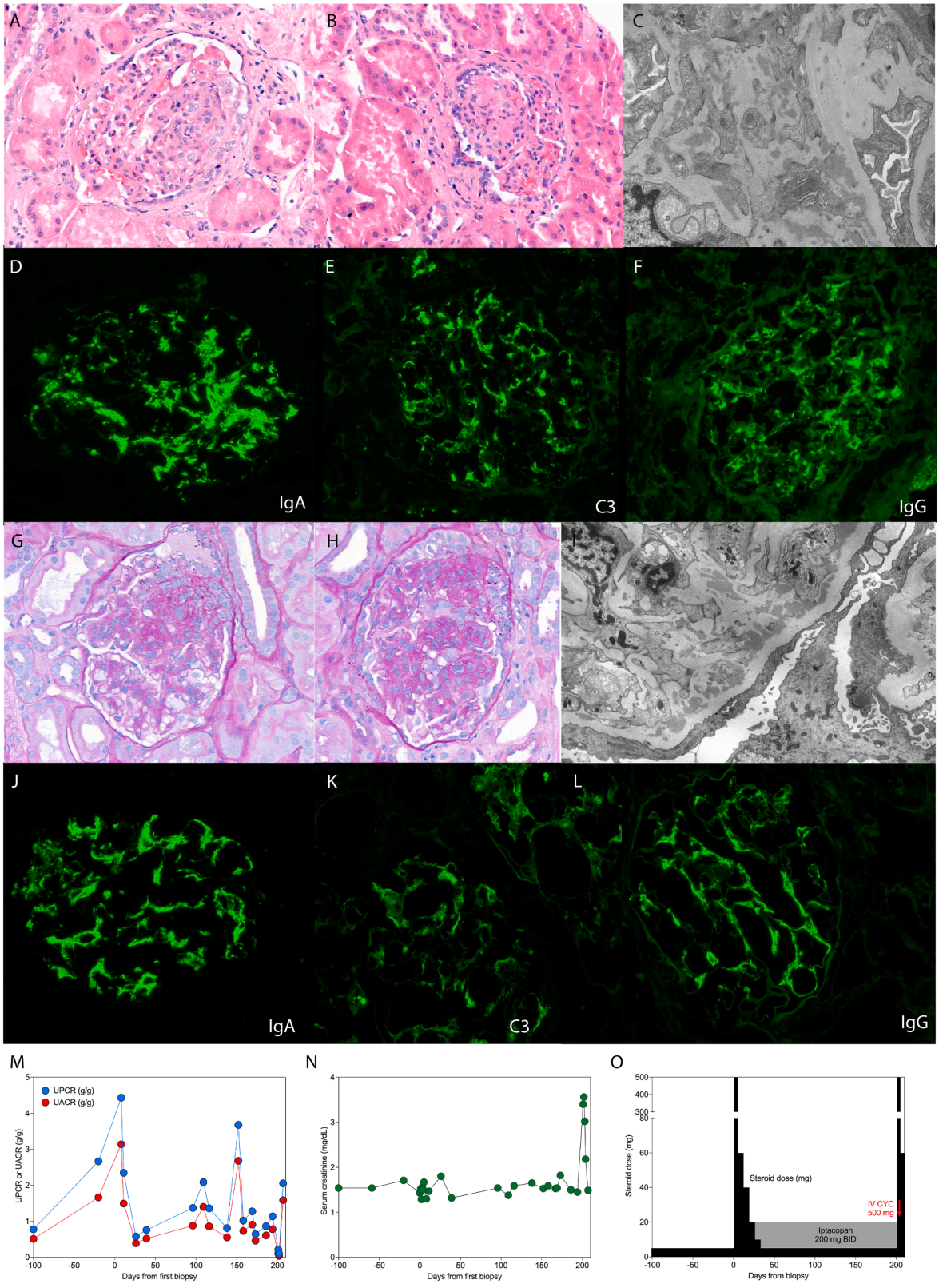

Figure 3. Third case of recurrent IgA nephropathy. (A, B) Light microscopy of the first posttransplant biopsy showed crescentic IgAN with collapsing features (40×, H&E stain). (C) Electron microscopy showed moderate foot process effacement (FPE) and mesangial electron-dense deposits (EDDs). (D) Immunofluorescence showed granular mesangial staining for IgA (4+), (E) C_3 (3+), and (F) IgG (3+). (G, H) Light microscopy of the second posttransplant biopsy showed persistently active crescentic IgAN with collapsing features (40×, PAS stain). (I) Electron microscopy showed moderate FPE, and EDDs mostly in the mesangial and subendothelial locations with rare subepithelial deposits. (J) Immunofluorescence showed mesangial staining for IgA (4+),

approved steroid-free immunosuppressive maintenance option for IgAN. He received MenB and MenACWY vaccines as well as penicillin prophylaxis. His kidney function remained at baseline.

After 4 months on iptacopan, his kidney function remained at baseline, but his microscopic hematuria persisted. His proteinuria decreased to less than 1 g/g initially then increased again with large fluctuations (UPCR 0.8-3.8 g/g, UACR 0.7-2.7 g/g). Of note, he reported intermittent methamphetamine use during this time. Given his persistent proteinuria, he underwent a repeat kidney allograft biopsy to reassess disease activity (Fig 3G-L). The biopsy showed persistently active crescentic IgAN with collapsing features (M1E1S1T0-C1). There was 5% GG and less than 10% IFTA. Immunofluorescence showed mesangial staining for IgA (4+), IgG (3+), C3 (3+), Kappa (3+), and Lambda (2+) but negative IgM and C1q staining. EM showed moderate FPE and EDDs mostly in the mesangial and subendothelial locations with rare subepithelial deposits. Given the persistent proteinuria and ongoing active glomerulonephritis on biopsy, he was planned for another course of glucocorticoids and intravenous cyclophosphamide (Euro-Lupus dosing) in addition to the iptacopan he was on.[5] While awaiting scheduling the intravenous cyclophosphamide, he developed clinical rapidly progressive glomerulonephritis with serum creatinine increasing to 3.6 mg/dL, which was treated successfully with intravenous steroids and cyclophosphamide (Fig 3M-O, Table 1).

DISCUSSION

Posttransplant recurrence of IgAN is common, estimated to be 23% at 15 years, and is associated with a higher risk of allograft loss.[3] Effective treatments for recurrent IgAN are urgently needed. Although the treatment landscape for IgAN in native kidneys has expanded significantly with the approval of sparsentan, atrasentan, targeted-release budesonide, and iptacopan, none of these approved treatments have been evaluated in clinical trials for recurrent IgAN after transplantation.

This report presents the first experience with iptacopan, a selective complement factor B inhibitor, in 3 KTRs with biopsy-proven recurrent IgAN. Iptacopan blocks the alternative complement pathway, which is involved in the pathogenesis of IgAN in native kidneys, but is not well studied in posttransplant recurrent IgAN.[6] Two of the three individuals demonstrated a significant reduction in proteinuria, suggesting that iptacopan, in combination with a short course of corticosteroids, may represent a promising therapeutic approach for selected patients with recurrent IgAN. This will require confirmation in larger studies.

The lack of response in the third individual may reflect a more aggressive or atypical disease phenotype. Notably, the index biopsy demonstrated both IgA and IgG deposits in the absence of an identifiable infection, raising the possibility of an atypical or overlapping form of IgAN less responsive to complement blockade alone. Although all three individuals received concomitant steroids, the observed response is unlikely to be explained by steroids alone, given (1) the lower dose and shorter duration used compared with the low-dose arm of the TESTING trial and (2) continued improvements in proteinuria even after prednisone discontinuation.[7]

None of the individuals in the study underwent changes to their transplant maintenance immunosuppression with iptacopan initiation. No infections occurred during follow-up. Importantly, all patients received meningococcal vaccination and were maintained on penicillin prophylaxis during iptacopan treatment because of attenuated vaccine responses in KTRs.

Several limitations should be acknowledged. These include the short duration of follow-up, the lack of protocol or repeat biopsies in the responders, and the absence of adherence biomarkers to confirm ongoing iptacopan use.

Although preliminary, these findings support further investigation of iptacopan in KTRs with recurrent IgAN. Future studies should evaluate long-term outcomes, histologic responses, and the potential benefit of combination therapies targeting additional pathogenic pathways, such as the BAFF/APRIL axis.

ARTICLE INFORMATION

Authors' Full Names and Academic Degree: Ayman Al Jurdi, MD, Abraham Cohen Bucay, MD, Pitchaphon Nissaisorakarn, MD, Hannah Gilligan, MD, Claire T. Avillach, MD, Veronica E. Klepeis, MD, PhD, Rex N. Smith, MD, PhD, Ragnar Palsson, MD, Kassem Safa, MD, Leonardo V. Riella, MD, PhD

Author's Affiliations: Department of Medicine, Nephrology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA (AAJ, ACB, PN, HG, RP, KS, LVR); Center for Transplantation Sciences, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA (AAJ, LVR); Vasculitis and Glomerulonephritis Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA (AAJ); Department of Pathology, Massachusetts General Hospital, Boston, MA (CTA, VEK, RNS).

Address for Correspondence: Dr. Ayman Al Jurdi, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston MA 02115. Email: aaljurdi@mgh.harvard.edu

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(K) C_3 (3+), and (L) IgG (3+). (M) Clinical course with trends of urine protein-creatinine ratio (UPCR, blue circles), urine albumin-creatinine ratio (UACR, red circles), (N) serum creatinine (green circles), and (O) treatment regimen.
Abbreviations: C3, complement component 3; EDDs, electron-dense deposits; FPE, foot process effacement; H&E, hematoxylin and eosin; IgAN, IgA nephropathy; IgG, immunoglobulin G; PAS, periodic acid–Schiff.

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