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Octreotide Delaying the Progression of Recurrent IgA Nephropathy After Kidney Transplantation

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Abstract: IgA Nephropathy (IgAN) is a common cause of end-stage kidney disease worldwide. Unfortunately, the exact pathogenesis of IgAN remains uncertain without any targeted therapy. While kidney transplantation remains the gold standard treatment for those with end-stage kidney disease from IgAN, recurrence occurs frequently and may lead to early kidney transplant loss. Research has suggested that insulin-like growth factor-1 may play a role in mesangial cell proliferation in IgAN and Somatostatin may inhibit insulin-like growth factor-1. In this single case study, we report the use of octreotide, a somatostatin analogue, as a potential novel therapy for early recurrent IgAN post kidney transplant.

(*Transplantation Direct* 2020;6: e518; doi: 10.1097/TXD.0000000000000963. Published online 24 December, 2019.)

IgA Nephropathy (IgAN) is the most common cause of primary glomerulonephritis in the world and a leading cause kidney disease.[1] The histological features of IgAN on kidney biopsy have been well described, including mesangial proliferation with mesangial IgA deposits.[1,2] The clinical features are variable and include a combination of proteinuria, hematuria, hypertension, and renal dysfunction.[1,3] Despite extensive investigation, the specific etiology of primary IgAN remains unclear, though likely multifactorial.[4-6] Without specific cause, the therapeutic approach remains limited and nonspecific.[7,8]

Kidney transplantation remains the gold standard treatment for IgAN, though disease recurrence posttransplant can have deleterious effects with limited, varying treatment approaches for recurrence.[9-11] The likelihood of recurrence posttransplant is increased with crescents on native kidney biopsy and presence of crescents on posttransplant allograft biopsies are associated with increased graft dysfunction.[12,13] Published literature has shown an increased expression of somatostatin receptors in kidney tissue of patients with IgAN, suggesting a possible role in pathogenesis of IgAN.[14] Further, insulin-like growth factor-1 (IGF-1) mitogenic activity is enhanced in IgAN, particularly in glomerular mesangial cells.[15] Interestingly, somatostatin has multiple roles including the inhibition of IGF-1.[16,17] Previous animal studies have shown the potential to use somatostatin analogs to delay the progression of chronic kidney disease, possibly through diminished proliferation of mesangial cells.[17-19] We hypothesized that IGF-1, with enhanced activity in IgAN and a possible mitogen for glomerular mesangial cell proliferation, may be inhibited using somatostatin analogues and this may blunt the progression of chronic kidney disease in IgAN. To our knowledge, we present our experience of the first reported use of Octreotide, a somatostatin analogue, to treat IgAN recurrence post kidney transplantation.

CASE REPORT

A Caucasian male was diagnosed with cresentic IgAN at the age of 28. After 5 months of hemodialysis, he underwent his first living related donor kidney transplant in October 2012 (3 antigen mismatch, cold and warm ischemia time 104/56 minutes, thymoglobulin induction with mycophenolate mofetil [MMF]/tacrolimus [TAC] for maintenance immunosuppression). Baseline serum creatinine (SCr) posttransplant was 1.6–1.9 mg/dL and this increased to 2.6 mg/dL with proteinuria and microscopic hematuria on posttransplant day 235 prompting kidney transplant biopsy that demonstrated recurrent IgAN (light microscopy with increased mesangial matrix/hypercellularity and immunofluorescence [IF] microscopy confirming recurrent

Received 16 September 2019. Revision received 23 October 2019.

Accepted 8 November 2019.

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The authors declare no funding or conflicts of interest.

A.S. and S.H. were involved in research design of case report, writing of the article, performance of the research for case report, and data analysis.

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).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000963

IgAN with +3 mesangial IgA staining) without evidence of rejection. He was treated with intravenous methylprednisolone (500 mg daily for 3 days) with taper, addition of oral prednisone, omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, and continued MMF/TAC. His kidney transplant function further deteriorated, oral Cyclophosphamide was added ~10 months posttransplant without success, and patient returned to hemodialysis on day 351 posttransplant.

Patient underwent his second living nonrelated donor kidney transplant in December 2014 as part of a paired exchange (cold and warm ischemia time 483/35 minutes, 5 antigen mismatch, calculated panel reactive antibody now 68%) with thymoglobulin induction therapy followed by maintenance immunosuppression (TAC/MMF/Prednisone). Baseline SCr remained between 1.3 and 1.6 mg/dL posttransplant without microscopic hematuria/proteinuria within first month. Patient underwent a surveillance kidney transplant biopsy on posttransplant day 22 that revealed histological recurrence of IgAN (mesangial matrix without increase in hypercellularity on light microscopy, but with mesangial IgA deposits on IF confirming recurrent IgAN) without rejection.

Alternative therapeutic modality was explored to delay the progression of IgAN. Octreotide, a somatostatin analogue, has been approved by FDA for the treatment of Acromegaly, Carcinoid Tumors, and Vasoactive Intestinal Peptide Secreting Tumors while also being used off-label for varying indications (eg, Hepatorenal Syndrome) and is generally well tolerated. To our knowledge, there has been no previous reported use of octreotide for the treatment of IgAN. First dose of Octreotide was administered with a single dose of 150 µg (subcutaneous) on posttransplant day 43 and then followed by a monthly maintenance dose (20 mg intramuscularly every month).

Kidney Transplant Function

Figure 1A, B illustrates progressive decline in kidney transplant function, measured by SCr and estimated glomerular filtration rate, with eventual failure of his first kidney transplant soon after the diagnosis of recurrent IgAN. In contrast, Figure 1C, D displays stable kidney transplant function for over 48 months despite early diagnosis of recurrent IgAN with his second kidney transplant.

Proteinuria

With second kidney transplant, proteinuria was detected early (0.94 urine protein creatinine ratio g/g at posttransplant day 302) and progressed to nephrotic range by posttransplant day 1095, as demonstrated in **Figure S1** (**SDC,** http://

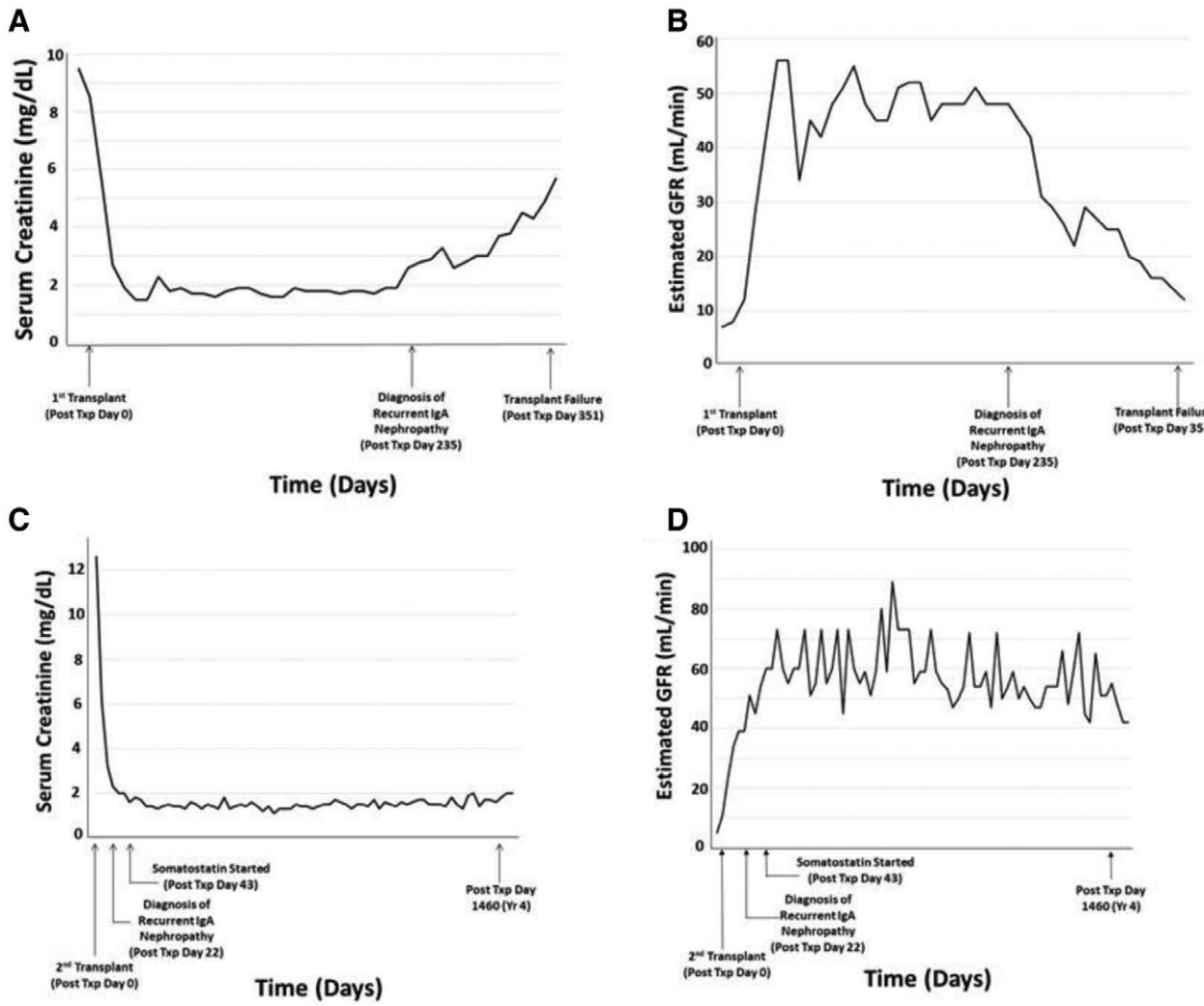

FIGURE 1. Kidney function temporal trend for first (A, B) and second (C, D) kidney tranplants

TABLE 1.

Histological scores for biopsies with first and second kidney transplant

Transplant/biopsy day posttransplant	g	i	t	v	ptc	cg	mm	ci	ct	cv	ah
First transplant—day 235	0	1	0	0	0	1	2	1	1	0–1	0
Second transplant—day 22	0	0	0	0	0	0	0	0	0	1	0
Second transplant—day 128	0	0	0	0	0	0	0	0	0	0	0
Second transplant—day 366	0–1	0–1	0	0	0	0	0	0	0	0	0

g, glomerulitis; i, interstitial inflammation; t, tubulitis; v, intimal arteritis; ptc, peritubular capillary inflammation; cg, chronic glomerular change; mm, mesangial matrix increase; ci, interstitial fibrosis; ct, tubual atrophy; ah, arteriolar hyalin.

links.lww.com/TXD/A231). Additionally, microscopic hematuria was detected on posttransplant day 128 and persisted throughout follow-up on surveillance urine analysis. Despite progressive proteinuria and persistent microscopic hematuria, patient's kidney transplant function remained stable at 48 months posttransplant with a SCr of 2.0 mg/dL and estimated glomerular filtration rate of 42 mL/min.

Kidney Transplant Histology

As part of his second transplant course, patient had a surveillance kidney transplant biopsy on posttransplant day 22 that showed recurrent IgAN by IF with granular mesangial IgA predominant deposition. Electron microscopy (EM) was notable for mesangial/paramesangial electron dense deposits. As per transplant center policy, patient had 3-month (on day 128) and 12-month (on day 366) protocol kidney transplant biopsies that continued to demonstrate IgAN recurrence by both IF and EM without any acute rejection, chronicity, or light microscopy findings suggesting increase in mesangial matrix as shown in Table 1.

Blood Pressure

For his second transplant course, his average systolic blood pressure was 129.9 ± 7.6 mm/Hg and diastolic blood pressure 67.4 ± 7.9 mm/Hg. This was lower than in comparison to his first transplant average systolic blood pressure of 146.5 ± 12.5 and diastolic blood pressure of 80.1 ± 8.9 ($P < 0.001$). Of note, angiotensin-converting enzyme inhibitor (ACEi) was not able to be used with first transplant course given rapid, progressive decline in renal function, though with second transplant, ACEi was started on posttransplant day 562.

Safety and Adverse Events

There were no adverse events from octreotide therapy (through 48 months). He did not develop BK viremia with either of his transplants or Donor Specific Antibody with his first transplant. He did develop weak, persistent Class I donor specific antibody ~2 years after his second transplant.

DISCUSSION

Lack of effective therapy for IgAN, both in native kidney disease and with recurrence post kidney transplant, can have harmful effects on long-term prognosis and remains an unmet need for patients with IgAN.[20] Here, we hoped that octreotide, a somatostatin analogue with a favorable side effect profile, could delay the progression of recurrent IgAN in a young patient with a previous devastating history of aggressive IgAN despite standard of care therapy. Our approach was based on previous evidence of somatostatin receptor upregulation in the mesangial cells of patients with IgAN suggesting a possible role of these receptors in the pathology of IgAN.[14,21] Moreover, in-vitro culture data suggest that IGF-1 activity, a key direct mediator of the effects of Growth Hormone, may be enhanced in glomerular mesangial cells and may play a role in the pathogenesis of IgAN.[15] We postulated that octreotide, a well-tolerated FDA-approved somatostatin analogue, may be effective in altering the pathogenesis of IgAN given its potential to inhibit IGF-1 and possibly decrease mesangial cell proliferation.

Now, we report that the use of octreotide may have diminished the impact of recurrent IgAN by extending kidney transplant survival to at least 4 years, including stable kidney transplant function over this period (as demonstrated in Figure 1C, D), which is dramatically different than his first kidney transplant course (Figure 1A, B). Further more, with the benefit of protocol biopsies, we demonstrate that despite early histological recurrence by EM and IF, there is minimal mesangial proliferation, glomerulitis, or development of renal allograft chronicity over the course of the first year posttransplant (Table 1). Additionally, with improvement in kidney transplant function, patient also had improved hemodynamics with his second kidney transplant, though he has had worsening proteinuria and persistent microscopic hematuria over the 4 year follow-up. Importantly, patient did not experience any adverse effects related to octreotide.

This single case report has limitations including solitary case, lack of control, absence of serum IgA/growth hormone/IGF-1 assessment, and lack of complement measurement, which is particularly gaining attention as possible therapeutic target in IgAN.[22] Further, while we suspect that early initiation of octreotide may have blunted mesangial proliferation from even developing, we cannot definitively ascertain this as biopsies were limited to the first year and not available further longitudinally. Additionally, earlier detection of recurrent IgAN, improved hemodynamics with ACEi, a possible more benign IgAN course with second transplant, addition of prednisone to maintenance IS regimen with second transplant, a nonrelated living donor with second transplant, and other mechanistic effects of octreotide (including but not limited to blunting of angiotensin II, potential anti-inflammatory and antiapoptotic renal effects of octreotide in ischemic states, and possible binding of overly expressed somatostatin receptors with unclear effect on mesangial cell function) also may explain improved course with second kidney transplant.[23-26] Still, in this case, there is a causal inference that octreotide may have blunted the course of recurrent IgAN. We hypothesize that octreotide, possibly through inhibition of IGF-1 resulting in blunted mesangial cell proliferation during the first year posttransplant and/or through other previously stated mechanistic effects, may have subsequently delayed progression of recurrent IgAN. Most importantly, despite his history of rapid

progression of IgAN both with his native kidney disease to end-stage kidney disease and recurrence in his first kidney transplant leading to early transplant loss, patient's kidney transplant function and survival was greatly enhanced with his second kidney transplantation. While not definitive, this case offers preliminary evidence to explore this approach further through basic and translational studies.

In conclusion, administration of octreotide, a somatostatin analogue, with early recognition of IgAN recurrence post kidney transplantation may have delayed the progression of recurrent IgAN. Further basic and translational studies are warranted to investigate the role of somatostatin analogue in IgAN.

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