2-1-2024

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Feasibility of Interleukin-6 Receptor Blockade in Cardiac Antibody-mediated Rejection

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Background. Antibody-mediated rejection (AMR) remains a significant cause of heart transplant mortality with few effective therapies. **Methods.** This study aimed to describe initial experience of using interleukin-6 receptor blockade with tocilizumab in the treatment of acute cardiac AMR at Barnes-Jewish Hospital/Washington University Transplant Center from July 2017 to May 2021 (n = 7). Clinical, echocardiographic, and serum alloantibody data were analyzed before and after treatment. **Results.** All participants demonstrated marked improvement in functional status. Echocardiographic data following 4–6 mo of tocilizumab revealed significant improvements in biventricular systolic function for all participants. Consistent reductions in donor-specific HLA or angiotensin type I receptor antibodies were not observed, suggesting that tocilizumab may act downstream of antibody production. No patient experienced drug-related complications that necessitated discontinuation of therapy. **Conclusions.** These findings provide initial insights into the safety and efficacy of interleukin-6 receptor blockade in the treatment of cardiac AMR and support the design of larger prospective studies.

(*Transplantation* 2024;108: 539–544).

INTRODUCTION

Antibody-mediated rejection (AMR) causes significant morbidity and mortality after heart transplantation. AMR has been linked to the development of cardiac allograft vasculopathy (CAV), a common cause of allograft failure.[1] AMR occurring >1 y after transplant portends a dismal prognosis, including a nearly 6-fold increase in the development of CAV.[2,3] AMR management is largely based on consensus recommendations. Treatment strategies focus on the removal of circulating donor-specific antibodies (DSAs), inhibition of DSA production, and minimization of complement-mediated endothelial injury.[4,5] Plasmapheresis (PP), IVIg, rituximab, eculizumab, and/or proteasome inhibitors have been utilized for treatment of cardiac AMR. Although retrospective studies suggest potential efficacy for these therapies, AMR remains a clinical challenge with high mortality.[2,3,6-8]

Interleukin-6 (IL-6) is a proinflammatory cytokine predominately produced by activated monocytes, macrophages, and endothelial cells with effects on innate and adaptive immunity. Relevant to AMR, IL-6 enhances plasma cell differentiation and survival, increases immunoglobulin secretion, stimulates differentiation of cytotoxic and T_H17 cells, and prevents apoptosis of antigen-specific T cells and differentiation of regulatory T cells.[9] IL-6 is also associated with atherosclerosis, cardiac hypertrophy, and myocardial fibrosis, indicating potential effects on vascular and myocardial remodeling.[10,11] Genetic deletion of IL-6 in mouse models of heart transplantation results in prolonged graft survival and reduced

Received 27 January 2023. Revision received 15 June 2023.

Accepted 28 June 2023.

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K.J.L. serves on the Medtronic DT-PAS/APOGEE trial advisory board and receives funding and unrelated sponsored research agreements from Amgen, Novartis, Implicit, and Kiniksa Biosciences. The other authors declare no conflicts of interest.

This work was supported by the Washington University in St. Louis Rheumatic Diseases Research Resource-Based Center grant (NIH P30AR073752), the National Institutes of Health [R01 HL138466, R01 HL139714, R01 HL151078, R01 HL161185, R35 HL161185], Leducq Foundation Network (#20CVD02), Burroughs Welcome Fund (1014782), Children's Discovery Institute of Washington University and St. Louis Children's Hospital (CH-II-2015-462, CH-II-2017-628, PM-LI-2019-829), Foundation of Barnes-Jewish Hospital (8038-88), and generous gifts from Washington University School of Medicine.

K.J.L. participated in the conceptualization. A.A.P., S.E.J., C.L., S.L., and J.D.S. participated in the investigation. A.A.P. and K.J.L. participated in writing, review, and editing. K.J.L. 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.transplantjournal.com).

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ISSN: 0041-1337/20/1082-539

DOI: 10.1097/TP.0000000000004784

CAV.[11-15] These observations suggest that IL-6 inhibition may have benefit in the treatment of AMR.

The IL-6 receptor antagonist tocilizumab has been successfully utilized in renal transplantation to decrease DSAs in highly sensitized transplant candidates and those experiencing AMR.[16,17] In the heart transplant population, tocilizumab has only been explored as a component of pretransplant desensitization protocols.[18] Herein, we report the first use of tocilizumab for treatment of cardiac AMR.

CASE DETAILS

We examined the efficacy and safety of tocilizumab in patients with acute cardiac AMR. Tocilizumab 8 mg/kg (maximum dose, 800 mg) IV was administered monthly. In patients who received PP near the time of tocilizumab initiation, the first dose of tocilizumab was administered after the completion of all PP sessions. We continued baseline immunosuppression with tacrolimus, mycophenolic acid and/or mammalian target of rapamycin inhibitor, and prednisone. Baseline demographic data and clinical characteristics are summarized in Table 1. Four patients received prior AMR treatment and had clinically refractory disease. DSA to HLAs or antiangiotensin II receptor type 1 (AT1R) antibody were measured at baseline and following 4–6 mo of tocilizumab (Table 2). Echocardiographic data following 4–6 mo of tocilizumab treatment was compared with baseline (Figure 1; **Table S1, SDC**, http://links.lww.com/TP/C866). The median (interquartile range) duration of tocilizumab was 15 (10–21) mo. Biopsy data and adverse effects are reported in **Tables S2 and S3** (**SDC**, http://links.lww.com/TP/C866), respectively. No patient experienced drug-related complications that necessitated discontinuation of therapy. We provide a detailed description of each case below with follow-up through December 2021. The study was approved by the Washington University Institutional Review Board. Written informed consent was not required.

Case No. 1

A 65-y-old Caucasian man who underwent heart transplant in October 2004 presented in June 2017 with worsening dyspnea. His posttransplant course was remarkable for AMR (pathological antibody-mediated rejection [pAMR] 1 I+) in November 2009 and CAV in 2015. Maintenance immunosuppression regimen consisted of cyclosporine (trough levels, 75–100 ng/mL), mycophenolate mofetil (1000 mg twice daily), and prednisone (5 mg daily).

Admission echocardiogram demonstrated left ventricle (LV) ejection fraction of 49% (reduced from 60% a year ago), diastolic dysfunction, and reduced right ventricle (RV) systolic function. Endomyocardial biopsy (EMB) showed chronic inflammation with subendocardial fibrosis (grade 1R). C4d stain was negative and CD68 stain showed scattered interstitial macrophages. He had several new class I and II DSA. Cardiac catheterization revealed elevated RAP (24 mm Hg), elevated pulmonary capillary wedge pressure (28 mm Hg), and reduced CI (1.27 L/min/m^2). Left heart catheterization (LHC) showed severe diffuse CAV. He received PP, IVIg, and rituximab (375 mg/m^2). His maintenance immunosuppression regimen was augmented to include tacrolimus, everolimus, mycophenolate mofetil, and prednisone.

TABLE 1.
Patient characteristics

Characteristics	Cohort (N = 7)
Age (y) at first tocilizumab dose, median (IQR)	50 (35–62)
Sex (male)	6 (85.7%)
Race	
White	3 (42.9%)
Black	4 (57.1%)
Maintenance immunosuppression	
Tacrolimus, MPA, prednisone	3 (42.9%)
Tacrolimus, MPA, mTOR inhibitor, prednisone	4 (57.1%)
Time from transplant to AMR (mo), median (IQR)	22 (11–40)
Time from transplant to tocilizumab initiation (mo), median (IQR)	25 (11.5–42)
Pre-tocilizumab PP	4 (57.1%)
Pre-tocilizumab IVIg	4 (57.1%)
Pre-tocilizumab rituximab	4 (57.1%)
Pre-tocilizumab biopsy findings	
pAMR0	0 (0%)
pAMR1, H+	2 (28.6%)
pAMR1, I+	1 (14.3%)
pAMR2	4 (57.1%)
Pre-tocilizumab ISHLT CAV grade	
0	2 (28.6%)
1	2 (28.6%)
2–3	1 (14.3%)
No assessment	2 (28.6%)
Duration of tocilizumab therapy (mo), median (IQR)	15 (10–21)
Post-tocilizumab biopsy findings	
pAMR0	3 (42.9%)
pAMR1	0 (0%)
pAMR2	0 (0%)
No assessment	4 (57.1%)
Post-tocilizumab ISHLT CAV grade	
0	2 (28.6%)
1	0 (0%)
2–3	5 (71.4%)
Last follow-up description	
Tocilizumab ongoing	4 (57.1%)
Tocilizumab discontinued because of adverse effects	0 (0%)
Tocilizumab discontinued because of other reasons	3 (42.9%)

AMR, antibody-mediated rejection; CAV, cardiac allograft vasculopathy; IQR, interquartile range; ISHLT, International Society for Heart and Lung Transplantation; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; pAMR, pathological antibody-mediated rejection grade (H: histology, I: C4d or CD68 immunostaining); PP, plasmapheresis.

He was readmitted 8 d later with progressive dyspnea, received additional PP and IVIg, and was discharged with plans for quarterly rituximab. Fifteen days later, he was readmitted and required dual inotropic support for maintenance of systemic perfusion. Given his progressive decline, tocilizumab was initiated.

During the first 6 mo after tocilizumab initiation, he was hospitalized once for dyspnea, which resolved with IV diuresis. After 6 mo of tocilizumab, echocardiogram showed improvement in LV and RV function with LVEF of 60%. HLA antibody screen showed persistent DSA (Table 2). He had stable NYHA class II-III symptoms. After 15 mo of tocilizumab, LHC showed severe CAV with disease progression involving the left circumflex artery and distal vasculature.

TABLE 2.

Antibody values for tocilizumab-treated patients

ID	Antibody detected (units)	Before tocilizumab	6 mo after tocilizumab initiation[a]
1	DQ3 (MFI)	23 387	21 175
	A26 (MFI)	22 954	5259
	A2 (MFI)	20 916	5849
	DR4 (MFI)	14 704	365
	B44 (MFI)	12 104	387
	DR53 (MFI)	7542	2244
	Cw5 (MFI)	7487	38
2	DQ8 (MFI)	22 147	24 419
	DR53 (MFI)	15 981	14 998
3	AT1R (U/mL)	>40	>40
4	DR53 (MFI)	12 594	21 425
	DQ2 (MFI)	8776	13 859
	DR51 (MFI)	5252	2301
	DR7 (MFI)	4925	2580
	B44 (MFI)	3373	3247
	DQ5 (MFI)	3293	93
5	None	—	—
6	DR53 (MFI)	17 742	2458
	DQ6 (MFI)	7201	632
	B7 (MFI)	2649	412
7	DQ7 (MFI)	19 038	11 069
	DQ2 (MFI)	18 688	6777
	DR53 (MFI)	8075	2578

[a] Data for patient 3 was obtained 4 mo after tocilizumab initiation.
AT1R, antiangiotensin II receptor type 1 antibody; MFI, mean fluorescence intensity.

To date, he has received tocilizumab for 54 mo. After nearly 4 y of monthly infusions, the frequency of tocilizumab infusions was changed to every 2 mo. He remains active and has had no further hospitalizations for heart failure.

Case No. 2

A 50-y-old African American man who underwent heart transplant in January 2017 presented in December 2018 with 2 wk of exertional dyspnea, fatigue, and activity intolerance. His posttransplant course was previously uneventful. Maintenance immunosuppression regimen consisted of tacrolimus (trough levels, 4–6 ng/mL) and mycophenolate mofetil (1000 mg twice daily).

Admission echocardiogram showed a marked decline in LV and RV systolic function compared with 3 mo prior with LVEF reduction from 64% to 15%. EMB showed moderate cellular rejection (grade 2R), and he had new DSA to DQ8 (mean fluorescence intensity [MFI]: 19 845), DR53 (MFI: 11 656), DR7 (MFI: 2967), and B57 (mean fluorescence intensity [MFI]: 2722). He received dobutamine for inotropic support, PP, IVIg, and rabbit antithymocyte globulin.

He was readmitted 48 h after discharge with volume overload. EMB demonstrated mild cellular rejection (grade 1R). C4d stain was negative and CD68 stain was positive. He had persistent DSA. He received a course of PP, IVIg, and rituximab 375 mg/m^2. His maintenance immunosuppression regimen was augmented with the addition of sirolimus and prednisone.

Approximately 4 wk later, he presented with increasing orthopnea, weight gain, and fatigue (NYHA class III symptoms). Echocardiogram showed persistent allograft dysfunction. EMB showed mild cellular rejection (grade 1R) with histologic features of AMR. He had persistently elevated DSA to DQ8 and DR53 (Table 2). LHC revealed no epicardial stenoses. Hemodynamic assessment demonstrated elevated LVEDP (35 mm Hg). Because of persistent allograft dysfunction and DSAs, tocilizumab was initiated.

Apart from a hospitalization for volume overload early after tocilizumab initiation, he had no further hospitalizations over the next 2 y. Echocardiogram 6 mo after tocilizumab initiation showed improved but persistent LV systolic dysfunction (LVEF = 32%) with grade III diastolic dysfunction. He had persistent DSA to DQ8 and DR53 (Table 2). However, his activity tolerance increased markedly (NYHA class I-II), and he was able to return to work and carry out daily activities without limitation. Beginning 6 mo after medication initiation, he developed serum elevations of ALT and AST to 2–3 times the upper limit of normal, which remained stable with continuation of therapy. The most recent LHC showed normal coronary arteries.

After 24 mo of tocilizumab, the patient was hospitalized for diverticulitis. Echo showed improved LV systolic function with LVEF 56%. Tocilizumab was discontinued in the setting of diverticulitis to reduce the possible risk of perforation. His LVEF has remained within the normal range.

Case No. 3

A 25-y-old Caucasian woman underwent heart transplant in October 2016 against a positive crossmatch and received PP, IVIg, and rabbit antithymocyte globulin without further evidence of rejection. She presented in April

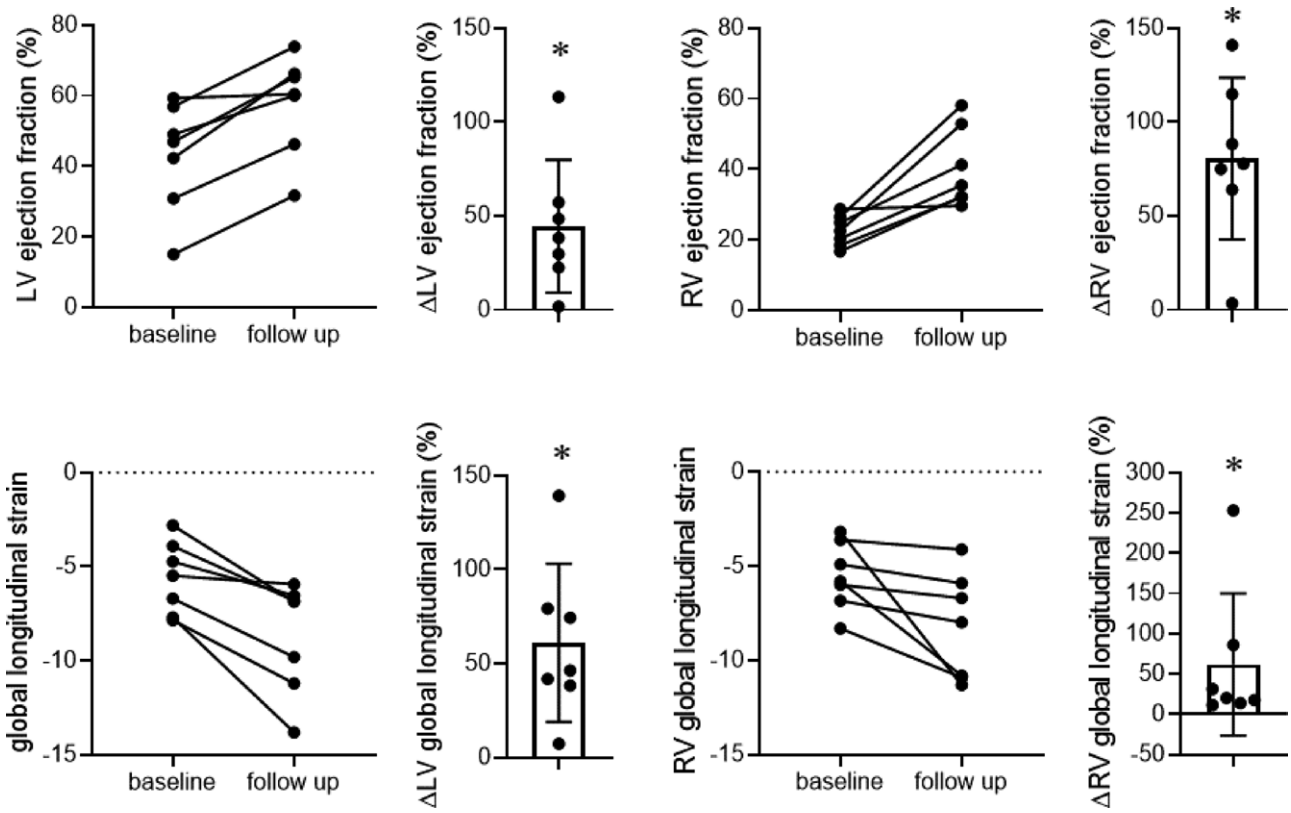

FIGURE 1. Echocardiographic measurements demonstrating improved LV and RV systolic function following tocilizumab treatment. Each data point represents an individual patient. Bars denote the mean values, and error bars indicate standard deviation. *P <0.05 compared to baseline (paired t-test, 2-tailed). RV ejection fraction was measured using the RV area method. LV, left ventricle; RV, right ventricle.

2019 with elevated resting heart rate. Her maintenance immunosuppression regimen consisted of tacrolimus (trough levels, 5–7 ng/mL), mycophenolate sodium DR (540 mg twice daily), and prednisone (5 mg daily). She received a brief course of sirolimus, which was discontinued with development of skin lesions.

Upon presentation, her ECG revealed atrial tachycardia. Echocardiogram showed a decline in LV and RV systolic function compared with 5 mo prior with LVEF reduction from 71% to 47%. EMB demonstrated mild perivascular and interstitial chronic inflammation without myocyte necrosis (grade 1R). HLA antibody screen was negative. She was treated with bolus steroids and her metoprolol XL dose was increased.

In July 2019, she presented with decreased activity tolerance, persistent abdominal bloating, lower extremity edema, and orthopnea (NYHA class III symptoms). Cardiac catheterization showed markedly elevated RAP (32 mm Hg), RVP (40/32 mm Hg), and pulmonary capillary wedge pressure (25 mm Hg). LHC was significant for distal CAV. EMB showed mild acute cellular rejection (grade 1R). No DSAs were detected. AT1R antibody testing revealed a high titer (>40 U/mL at 1:100 dilution). She was admitted for treatment of AMR and received dobutamine, PP, IVIg, and tocilizumab. Irbesartan was initiated, and her maintenance immunosuppression was adjusted with initiation of everolimus and discontinuation of mycophenolic acid. Echocardiogram prior to discharge showed persistent allograft dysfunction (LVEF = 47%).

Approximately 6 wk after discharge, she was admitted with shortness of breath, abdominal distension, and weight gain, which resolved with IV diuresis. She did well for the next 3 mo without any subsequent hospitalizations. She reported activity tolerance improvement (NHYA class II symptoms) and repeat echocardiogram after 4 doses of tocilizumab showed normal LV systolic function (LVEF = 65%). AT1R remained >40 U/mL at 1:100 dilution. Unfortunately, 5 mo after initiating treatment, she was found unresponsive at home. Autopsy showed severe CAV without evidence of infection, myocardial infarction, cellular rejection, or AMR.

Case No. 4

A 62-y-old African American man who underwent heart transplant in January 2020 for AL cardiac amyloidosis presented in June 2020 with fatigue and worsening dyspnea. His posttransplant course was relatively unremarkable, except for recent coronavirus 2019 infection, which was managed conservatively in the outpatient setting. Maintenance immunosuppression regimen consisted of tacrolimus (trough levels, 6–8 ng/mL), mycophenolate mofetil (500 mg twice daily), and prednisone (5 mg daily).

Admission echocardiogram showed normal systolic function but restrictive diastolic function with increased myocardial wall thickness compared to prior studies. EMB showed mild to focally moderate interstitial and perivascular chronic inflammation. C4d and CD68 staining were positive. Congo red stain was negative for amyloid. He had several new class I and II DSA. He received PP, IVIg, and rituximab (375 mg/m^2). His maintenance immunosuppression was adjusted with initiation of sirolimus and discontinuation of mycophenolate mofetil.

He was readmitted 1 wk later with ongoing symptoms and EMB results consistent with persistent AMR (pAMR2) and negative congo red staining. HLA antibody screen showed persistent class I and II DSA (Table 2). He received an additional course of PP and IVIg, and tocilizumab was initiated.

After 6 mo of tocilizumab, echocardiogram showed normal LV size and function (LVEF = 74%) and normal RV size with mild hypokinesis. HLA antibody screen showed persistent DSA (Table 2). He had stable NYHA class II symptoms and persistent diastolic dysfunction.

The patient did not require any subsequent hospitalizations until July 2021, when he presented with generalized malaise and worsening dyspnea on exertion. EMB results were consistent with chronic AMR and HLA antibody screen revealed persistent DSA. He was treated for recurrent AMR with bolus steroids, PP, IVIg, and tocilizumab (continuation of therapy). LHC demonstrated severe CAV of the LAD and PDA, which had significantly progressed from 6 mo prior. He underwent PCI to the LAD.

To date, he has received tocilizumab for 18 mo. Given persistent leukopenia/neutropenia, a single dose of tocilizumab was held in January 2021. Cell counts did not improve with interruption of therapy, and monthly tocilizumab was resumed. Unfortunately, he has experienced recurrence of his AL amyloidosis without cardiac involvement. He has stable allograft function and NYHA class II symptoms.

Case No. 5

A 42-y-old African American man who underwent heart transplant in January 2020 presented in July 2020 with fatigue, dyspnea, worsening volume overload, and abdominal bloating. His posttransplant course was previously uneventful. Maintenance immunosuppression regimen consisted of tacrolimus (trough levels, 6–8 ng/mL), mycophenolate mofetil (1000 mg twice daily), and prednisone (5 mg daily).

Admission echocardiogram showed a marked decline in LV and RV systolic function compared with 2 wk prior (LVEF decreased from 45%–50% to <30%). EMB showed morphological features concerning for AMR. C4d stain was negative, but CD68 stain was positive. DSA screen and AT1R antibody testing were negative. He received dobutamine for inotropic support, PP, IVIg, and tocilizumab. His maintenance immunosuppression was adjusted with initiation of sirolimus and discontinuation of mycophenolate mofetil.

Following initiation of tocilizumab, the patient did well in the outpatient setting over the next 6 mo. Echocardiogram 6 mo after tocilizumab initiation showed LVEF = 46%.

Approximately 1 y after tocilizumab initiation, he was admitted with volume overload and concern for rejection. EMB was negative for ACR or AMR. LHC demonstrated severe 3-vessel CAV, which had significantly progressed from 9 mo prior. He underwent PCI to the RCA and LAD. Tocilizumab was discontinued at that time.

Case No. 6

A 28-y-old African American man who underwent heart transplant in May 2019 presented in September 2020 with worsening dyspnea. His posttransplant course was previously remarkable for cytomegalovirus pneumonitis and retinitis (January 2020) and acute 3R rejection (March 2020) which was treated with bolus steroids and antithymocyte globulin. Maintenance immunosuppression regimen consisted of tacrolimus (trough levels, 3–5 ng/mL), everolimus (trough levels, 2–3 ng/mL), and prednisone (5 mg daily).

Admission echocardiogram showed increased LV wall thickness and severe diastolic dysfunction. EMB demonstrated reactive endothelial cells and minimal cellular rejection (1R). C4d stain was negative and CD68 stain showed scattered interstitial and perivascular macrophages. HLA antibody screen was remarkable for DSA to DR53 (MFI: 17 742), DQ6 (MFI: 7201), and B7 (MFI: 2549). He received dobutamine for inotropic support, PP, IVIg, and tocilizumab.

Following initiation of tocilizumab, the patient has not required any hospitalizations. Echocardiogram 6 mo after tocilizumab initiation showed preserved LVEF, reduced LV wall thickness, and improved diastolic function. HLA antibody screen showed notable improvement in DSA (Table 2).

He has been receiving monthly tocilizumab for 15 mo and has NYHA class I symptoms with stable allograft function. The most recent LHC performed in June 2021 showed normal coronary arteries.

Case No. 7

A 62-y-old Caucasian man who underwent heart transplant in February 2017 presented in March 2021 with worsening dyspnea. His posttransplant course was previously uneventful from a cardiac standpoint. Maintenance immunosuppression regimen consisted of tacrolimus (trough levels, 4–6 ng/mL) and mycophenolate mofetil (500 mg twice daily).

Admission echocardiogram showed reduced LV systolic function and marked diastolic dysfunction. EMB demonstrated pAMR2 with possible concurrent cellular rejection. He had several new class I and II DSA. LHC revealed mild CAV with distal pruning and slow coronary filling. He was treated with bolus steroids, PP, IVIg, and rituximab (375 mg/m^2). His maintenance immunosuppression regimen was adjusted with the addition of sirolimus and prednisone and the discontinuation of mycophenolate mofetil.

He was readmitted 1 mo later with ongoing fatigue and dyspnea on exertion. Echocardiogram showed reduced LV systolic function (LVEF = 40%–45%) and restrictive diastolic dysfunction. EMB demonstrated evidence of persistent AMR (pAMR2) and HLA antibody screen showed persistent DSA to DQ7, DQ2, and DR53 (Table 2). He received an additional course of bolus steroids, PP, and IVIg, and tocilizumab was initiated.

Apart from a hospitalization for volume overload early after tocilizumab initiation, he has not required any subsequent hospitalizations. Echocardiogram 6 mo after tocilizumab initiation showed normal LV systolic function (LVEF = 65%) and normal diastolic function. DSA screen showed a modest reduction in DSA (Table 2). LHC showed severe CAV with high grade lesions in the proximal LAD and ramus intermedius. He subsequently underwent PCI to the LAD and the ramus.

He continues to receive monthly tocilizumab. To date, he has received 8 doses, and he has stable allograft function and NYHA class I symptoms.

DISCUSSION

This case series offers initial evidence of safety and efficacy for tocilizumab in the treatment of AMR in heart transplant recipients. All participants reported improvements in functional capacity (NYHA functional classification). Notably, 4 patients had refractory AMR (resistant to PP, IVIg, and rituximab) before receiving tocilizumab. Echocardiography provided objective evidence of sustained improvement in allograft function. These changes were typically observed after 2–3 mo of therapy, suggesting a delayed mechanism of action.

There was no consistent effect of tocilizumab on DSA titer or CAV. As this is a single-arm study, we cannot eliminate the possibility that tocilizumab slowed the progression of CAV, reduced the total antibody burden, or prevented the production of new DSA. However, these findings suggest that tocilizumab may exert its effects downstream of antibody production, potentially through reducing endothelial cell and/or intravascular macrophage activation and effector cytokine production. It is also possible that tocilizumab has direct effects on myocardial injury and/or LV remodeling as was evident in the context of acute myocardial infarction.[19]

Tocilizumab was generally well tolerated, but our experience demonstrates the importance of careful monitoring with its use. Bone marrow suppression occurred in some cases, but no bleeding or serious infections were observed. One patient was noted to have mild transaminitis, which began 6 mo after initiation of tocilizumab and remained stable. This is consistent with previous literature that indicates serum aminotransferase elevations may occur with tocilizumab, but do not worsen with repeated exposures.[20] The same patient later developed diverticulitis. Since tocilizumab has been associated with gastrointestinal perforation, we chose to discontinue therapy. Patients at our center are prescreened for gastrointestinal issues and monitored closely for the development of symptoms with tocilizumab use. Interestingly, no patient in our study experienced notable infectious events during follow-up.

Limitations of this case series include the small sample size and single-arm experience. Patients were heterogeneous with respect to AMR etiology, presentation, and background treatment regimens. Given the absence of a control group, we cannot definitively conclude that tocilizumab was solely responsible for the observed improvements in allograft function. However, our findings provide clinical data to support future prospective randomized trials to assess the utility of tocilizumab for the treatment of AMR in heart transplant recipients. A study investigating tocilizumab in the first year after heart transplantation may also provide important insights (NCT03644667).

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