BIOMATRIX
Specialty Infusion Pharmacy

A Revised Assessment of Three-Year Outcomes Points to Transplant Success in Sensitized Patients Receiving a Standardized Desensitization Therapy

Introduction

With a goal to develop a safe, effective, and consistent approach to desensitization therapy using IVIG, BioMatrix has partnered with 34 renal transplant programs in the United States. Starting in 2011, we instituted a standard-of-care protocol for desensitization in patients awaiting a transplant with antibodies reactive to HLA antigens present in their serum. We have long known that having these pre-transplant HLA antibodies make donor selection difficult, because transplanting across a HLA antibody can lead to early acute rejection post-transplant and early allograft loss (1-7). However, prior to 2011, transplant centers around the world have implemented various versions of desensitization protocols. Many of these protocols use intravenous immune globulin (IVIG). However, not all desensitization protocols with IVIG are the same.

In 2016, we reported our three-year results showing that using one protocol in a large number of patients, we have strong evidence to create more uniform desensitization guidelines for sensitized patients. Our desensitization protocol with IVIG allows patients to reach transplant with a low risk of AMR and excellent allograft function post-transplant. Since 2011, 421 patients have started desensitization therapy under this program. As of September 2016, 60 patients were still receiving desensitization and awaiting a transplant. Within the remaining 361 patients, 111 had reached transplant, achieving an effective transplant rate of 30.7% (Table 1). In all, 250 patients were discontinued from the desensitization program (67% were discontinued from therapy in the first six months). Of those who did not complete desensitization, the major reasons were the following (Table 1): inadequate response to treatment (32%), physician did not continue the IVIG therapy (16%), patient choice (9%), noncompliance (4%), loss of intravenous access (6%), medical issues unrelated to IVIG administration (10%), and issues with insurance coverage (4%).

We believe three of the reasons for discontinuation, a) medical issues unrelated to IVIG administration, b) noncompliance, and c) issues with insurance coverage, are unrelated to the therapeutic success of the protocol. Therefore, we, herein, conducted a revised ad-hoc analysis of the 2016 data. We have chosen to exclude those patients (n=45) from analysis to get a clearer view of the success of the protocol.

Methods

Desensitization therapy

All patients received desensitization therapy consisting of IVIG at a weight based dose of 2 grams/kilogram per month (i.e. high dose IVIG). In addition, 11 patients also received concomitant rituximab therapy, and two patients received bortezomib therapy.

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Post-transplant data collection

Post-transplant follow-up laboratory, biopsy, and graft status data collection were done by contacting the transplant center coordinators or obtaining results via laboratory services as part of normal transplant care. Glomerular filtration rate (eGFR via modification of diet in renal disease (MDRD) study equation (8, 9)) was recorded at the date of last follow-up. Graft failure, antibody mediated rejection patients were excluded from post-transplant analyses if they were considered lost to follow-up post-transplant or if an eGFR was not obtainable at last follow-up (n=26).

Statistical analysis

All statistical analyses were performed using Stata/MP version 14.1 (College Station, Texas). Kaplan-Meier analysis was used to determine probability of survival.

Results

Three hundred sixteen patients received desensitization and were either transplanted or discontinued for reasons other than a) medical issues unrelated to IVIG administration, b) noncompliance, and c) issues with insurance coverage. Of these 316, 111 have reached transplant, achieving an effective transplant rate of 35% (Table 1).

Transplantation and outcomes

Within the 111 patients who reached transplant, the median time to transplant was 7.5 months (range 9 days to 41 months) following start of IVIG desensitization. The transplant recipients were primarily female (Table 2). The majority of patients received a re-transplant (61%). Sixty-three percent of transplanted patients received one to six monthly doses of IVIG prior to transplant. Eighty-six percent of all transplanted recipients were desensitized using high dose IVIG alone.

In the transplanted patients with reported follow-up (n=85), four (5%) have experienced antibody mediated rejection (AMR) episodes to date (Table 3). All AMR occurred in the first-year post-transplant. Two patients experienced acute cellular rejection. In comparison to other desensitization program results, the AMR rate of 5% is much lower than the average AMR rate (26%) reported across major high dose IVIG desensitization programs.(1-7)

Graft survival post-transplant remains excellent during the follow-up period in this cohort of 85 patients (Figure 1). Five patients have experienced allograft failure (6%). One-, two-, and three-year survival rates were 96%, 94%, and 90%, respectively. Two transplants failed immediately during transplant (primary non-function). The cause of allograft loss in the remaining three cases was chronic alloantibody mediated rejection (CAMR). Death with a functioning graft occurred in three patients due to infection/sepsis. To date, the graft survival rate in this deceased donor transplant population receiving desensitization is better than other reports (78-91% survival).(1-7)

In the patients that received a transplant, are still alive, and still have a functioning allograft (n=77), graft function remains excellent. In the 14 patients that have crossed the three-year post-transplant time-point, the median eGFR at last follow-up is 42.5 mL/min/1.73m2. Only 1 out of 14 had an eGFR below 30 mL/min/1.73m2. In the 21 patients that are between two and three years post-transplant, the median eGFR at last follow-up is 55 mL/min/1.73m2. Only 2 out of 21 had an eGFR below 30 mL/min/1.73m2. In the remaining 42 patients with less than two years of follow-up, the median eGFR at last follow-up is 55 mL/min/1.73m2.

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Reasons for stopping desensitization

Although many patients reached transplant following successful desensitization, 205 patients were discontinued from the desensitization program. Of those who did not complete desensitization, the major reasons were the following (Table 1): inadequate response to treatment (39%), physician did not continue the IVIG therapy (20%), patient choice (11%), and loss of intravenous access (7%). Death occurred in three patients and was unrelated to the therapy. An adverse event was the reason for discontinuation of IVIG administration in 16% of patients. The adverse events reported consisted of hypertension, headache, thrombocytopenia, hemolytic anemia, low platelets, and chest tightness.

Discussion

Revision of the analysis suggests that a slightly higher rate of transplantation occurred based on this standardized protocol. Achieving a transplantation rate after desensitization of 35% is among one of the highest reported. In addition, we still are impressed by the fact that desensitization with IVIG can allow patients to reach transplant with a low risk of AMR and excellent allograft function, post-transplant. By using one protocol in a large number of patients, we feel that we have strong evidence to create more uniform desensitization guidelines for sensitized patients.

Contributions:

Charlotte Prohaska, RN (BioMatrix) coordinated data collection with the transplant centers and laboratories. Matthew J. Everly, PharmD, BCPS, FAST (Independent Consultant) analyzed the data and drafted the manuscript.

Table 1. **Desensitization Outcomes**

	DESENSITIZED SUBJECTS (N=316)*
Patient was transplanted, n (%)	111 (35)
Patient discontinued desensitization, n (%)	205 (65)
Therapeutic reasons for desensitization discontinuation, n (% of discontinued patients)	
Inadequate response to therapy	80 (39)
Physician did not continue therapy	40 (20)
Adverse event related to desensitization	32 (16)
Patient choice	23 (11)
Loss of intravenous access	15 (7)
Other	15 (7)

**excludes 60 patients still receiving desensitization*

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Table 2. **Transplanted Patients**

	TRANSPLANTED SUBJECTS (N=111)
Recipient characteristics	
Median age at transplant (range)	47 (22-80)
Female, n (%)	71 (64)
Median BMI at transplant (range)	26 (13-40)
Re-transplants, n (%)	68 (61)
Caucasian recipient, n (%)	50 (45)
Primary insurance coverage for desensitization therapy	
Medicare part D, n (%)	86 (77)
Medicaid, n (%)	1 (1)
Commercial, n (%)	24 (22)
Recipient pre-transplant diagnosis	
Lupus nephrits, n (%)	6 (5)
FSGS, n (%)	13 (12)
Diabetic nephropathy, n (%)	9 (8)
Hypertension, n (%)	94 (85)
Sensitization history	
Re-transplants, n (%)	68 (61)
Transfusion, n (%)	104 (93)
Previous pregnancy, n (%)	58 (52)
Dialysis characteristics	
Preemptive transplant, n (%)	4 (4)
Median time on dialysis, (range)*	73 (3-310)
Transplantation characteristics	
Deceased donor, n (%)	104 (94)
Living donor, n (%)	7 (6)

**out of 100 cases, BMI=body mass index, FSGS=focal segmental glomerulosclerosis*

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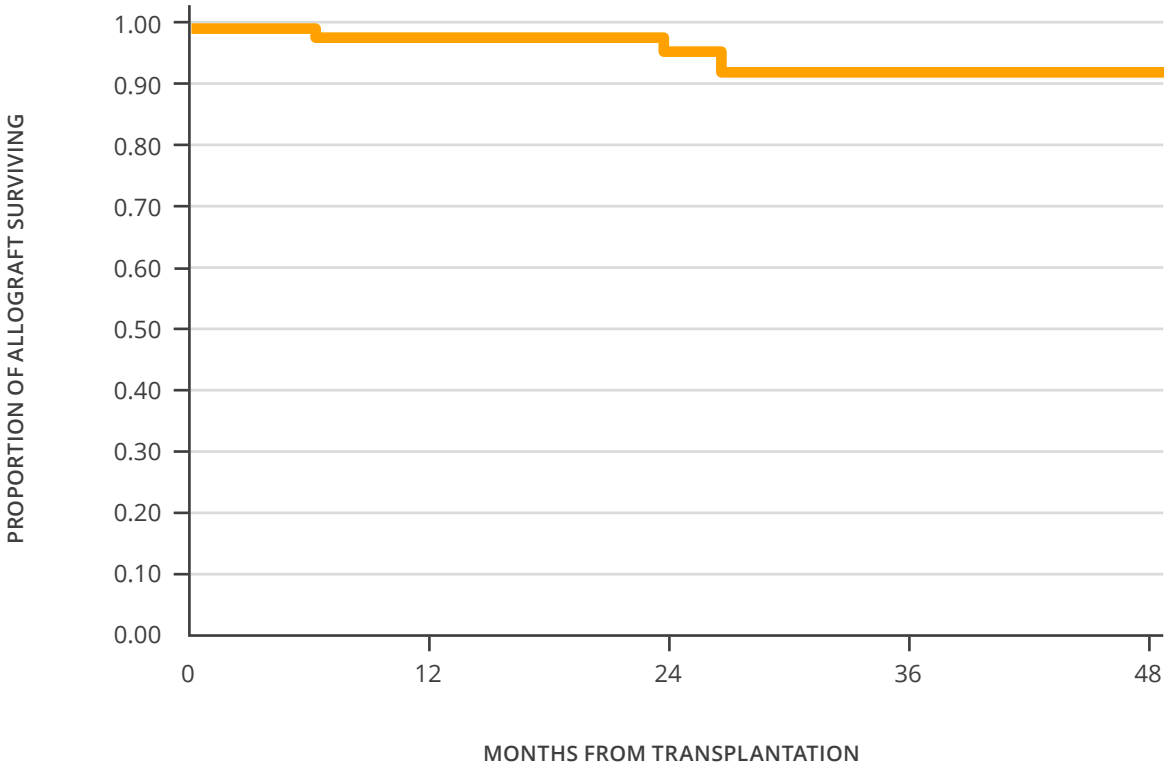
Table 3. **Post-transplant Allograft Outcomes**

	TRANSPLANTED SUBJECTS (N=85)
Acute Rejection, n (%)	7 (8)
AMR, n (%)	4 (5)
CAMR, n (%)	2 (2)
Allograft failure, n(%)	5 (6)
Patient death, n (%)	3 (4)
Median months of post-transplant follow-up (range)†	20 (1-49)

† excluding allograft loss cases, AMR= alloantibody mediated rejection, CAMR=chronic alloantibody mediated rejection

Fig 1. **Post-transplant Allograft Survival (n=85)**



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