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The Journal of
Heart and Lung
Transplantation

http://www.jhltonline.org

RESEARCH CORRESPONDENCE

Peri-operative desensitization for highly sensitized heart transplant patients

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Heart transplantation remains the "gold standard" for the management of end-stage heart failure. Transplantation of sensitized patients has increased over the past 25 years.[1] With more patients being bridged with durable ventricular assist devices (VADs), improved survival of the congenital heart disease population and increased re-transplantation, the pool of sensitized patients eligible for transplant is expected to rise.[2] Patients with circulating human leukocyte antigen (HLA) antibodies face increased waitlist mortality owing to the longer time required to find an acceptably mismatched donor. These patients are also more likely to have clinical deterioration with longer waitlist times, potentially rendering them transplant-ineligible.

To improve access to organs for this vulnerable population, the Canadian Cardiac Transplant Network changed the listing strategy in 2012 to prioritize highly sensitized cardiac patients, defined in this context as those with calculated panel reactive antibodies (cPRA) ≥80% (noted for allocation purposes as Status 4S). This strategy has allowed national sharing of donors (after medically high status) for these highly sensitized candidates, allowing them access to an increased absolute donor pool.[3]

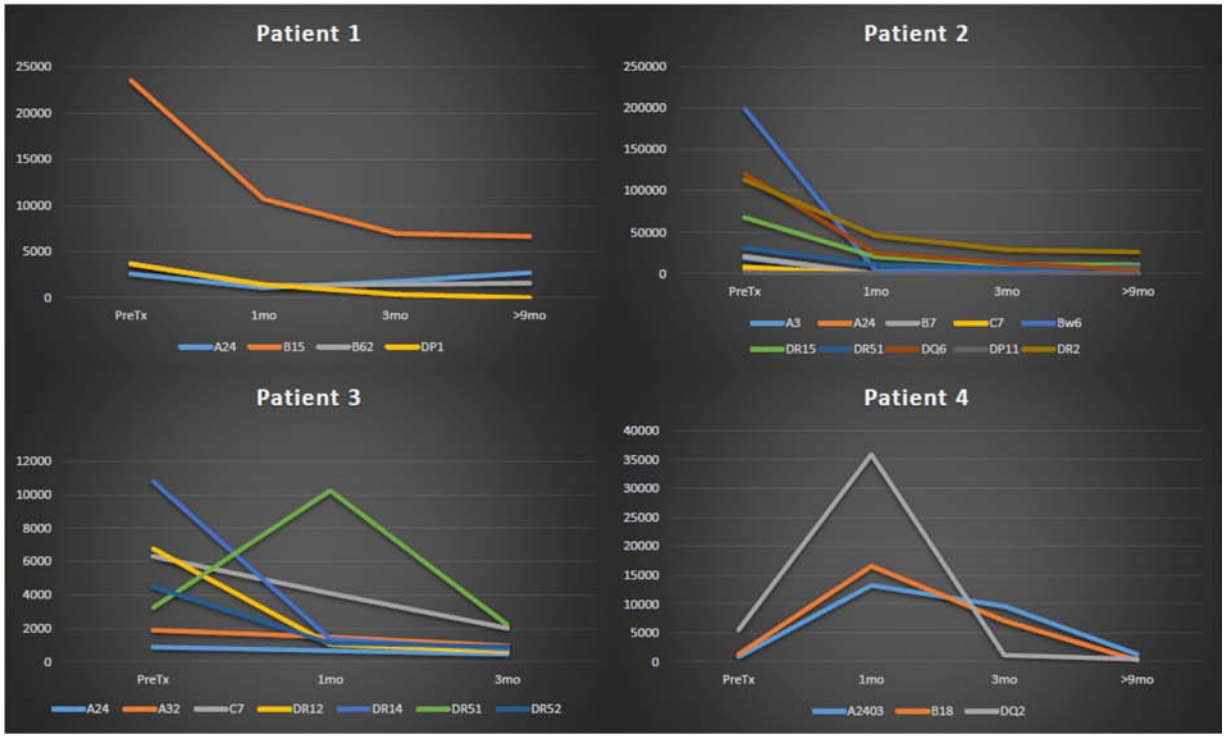

Figure 1 Individual mean fluorescence intensity (MFI) trends for donor-specific antibodies (DSA). The scale for each patient varies as it is driven by the individual MFI DSA maximum.

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https://doi.org/10.1016/j.healun.2017.12.005

Table 1 Baseline Characteristics of Highly Sensitized Patients Requiring Desensitization

	Patient 1	Patient 2	Patient 3	Patient 4
Age at Tx (years)	27	55	43	51
Sex	F	F	F	F
Blood group	O^+	O^+	O^+	O^+
cPRA pre-Tx (Class I/II)	95/3	98/95	92/85	100/84
Support pre-Tx	HeartMate II LVAD	HeartWare LVAD	High-dose milrinone	Systemic RV HeartWare
Time on the waitlist (days)	1,554	71	1,551	868
Etiology of cardiomyopathy	Idiopathic cardiomyopathy	Idiopathic cardiomyopathy	Familial dilated cardiomyopathy	Transposition of the great arteries post–Mustard procedure and systemic RVAD
Pre-transplant co-morbidities	Left brachial artery embolism; chronic drive-line infection; LVAD thrombus treated medically; multiple sclerosis; vaginal bleeding	ASD with device closure; pulmonary embolism; cardiac standstill on inotropes; severe RV failure	AF	SVC baffle stent; paroxysmal atrial fibrillation; hypertension
CMV status	D^-/R^+	D^-/R^+	D^-/R^-	D^+/R^-
Total ischemic time (min)	300	139	167	300
Cross-clamp time	NA	175	156	NA

AF, atrial fibrillation; ASD, atrial septal defect; CMV, cytomegalovirus; cPRA, calculated panel reactive antibodies; D, donor; LVAD, left ventricular assist device; NA, not applicable; R, recipient; RV, right ventricular; RVAD, right ventricular assist device; SVC, superior vena cava; Tx, transplant.

Although implementation of Status 4S in allocation has translated into successful donor-specific antibody (DSA)-negative transplantation of more highly sensitized patients,[3] these patients still face barriers to transplant. To be eligible for 4S-based allocation and the national pool of donors under current policy (and to ensure equitable access via use of the Status 4S between different regions), patients require a negative virtual crossmatch to a proposed donor using both current and historical antibodies, which for some very highly sensitized (cPRA >95%) patients may be a rare to non-event during their wait time in a country with few cardiac donors per year. It is therefore recognized that, for some candidates, transplant opportunities may be more available by means of desensitization strategies. In general terms, desensitization protocols remove circulating HLA antibodies and target production of antibodies before or at the time of transplantation. Outcomes of desensitization are drawn mostly from the renal transplantation literature with few systematic studies in heart and lung transplantation. The absence of randomized clinical trial data is reflected in the

Table 2 Flow Cytometry Crossmatch and DSA MFI[a]

				Sum MFI		
Patient	DSA	FCXM	Pre-Tx	1 month	3 months	9 to 12 months
1	A24 B62(B15)	TC: positive; CS: 238; MFIr: 8.5	Class I: 26,133	11,761	8,732	9,339
	DP1	BC: positive CS: 109; MFIr: 2.67	Class II: 3,260	1,540	345	Negative
2	A3 24 Bw6(B7) C7	TC: strongly positive; CS: 697; MFIr: 112	Class I: 232,868	3,957[b]	3,721[b]	0
	DR15 DRw51 DQ6 DP11	BC: strongly positive; CS: 545; MFIr: 165	Class II: 198,506	56,801	40,884	24,405
3	A24 32 C7	TC: positive CS: 132; MFIr: 3.43	Class I: 9,090	6,260	3,420	Not yet achieved
	DR12 14 DRw51 52	BC: strongly positive; CS: 283; MFIr: 12.76	Class II: 25,300	13,754[c]	4,463	Not yet achieved
4	A2403 B18 C12	TC: weakly positive; CS: 101; MFIr: 6.1	Class I: 2,920	29,849[d]	16,728	1,571
	DQ2	BC: positive; CS: 144; MFIr: 3.65	Class II: 5,450	35,864[d]	1,171	449

BC, B cell; CS, channel shift; DSA, donor-specific antibodies; FCXM, flow cytometry crossmatch; MFI, mean fluorescence intensity; MFIr, MFI ratio (on a flow crossmatch); pre-Tx, pre-transplant; TC, T cell.

[a]MFIs are not quantitative and do not represent titer or antibody amount. They are reported herein for general trend interpretation.

[b]Sum MFI includes all Bw6 beads in the single-antigen bead (SAB) reaction for transparency; however, all Bw6 beads were below threshold for positive and would not have been reported as DSA at 3 or 6 months.

[c]For information only. Additional DQ6 DSA at 7,728 MFI at 1 month post-transplant may also represent memory response indicative of sensitization to this antigen pre-transplant not detected in pre-transplant screening, as a primary dnDSA immunoglobulin G response commonly takes longer to be detected.

[d]Despite weakly positive crossmatch and lower level DSA, robust memory response at 1 month post-transplant confirms pre-transplant DSA as relevant.

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