Panel-Reactive Screening and Treatment Practices Following Bridge to Transplantation Ventricular Assist Device Placement

Ronald S. Freudenberger MD
Lehigh Valley Health Network, ron.freudenberger@lvhn.org

Isaac Tawfik

M Shinnar

T Pendergast

Published In/Presented At

Freudenberger, R., Tawfik, I., Shinnar, M., & Pendergast, T. (2009). Panel-reactive screening and treatment practices following bridge to transplantation ventricular assist device placement. *Transplantation Proceedings*, *41*(5), 1813-1815. doi:10.1016/j.transproceed.2009.03.062

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Panel-Reactive Screening and Treatment Practices Following Bridge to Transplantation Ventricular Assist Device Placement

R.S. Freudenberger, I. Tawfik, M. Shinnar, and T. Pendergast

ABSTRACT

The use of left ventricular assist devices (LVAD) as a bridge to transplantation is associated with the development of circulating antibodies. We conducted a survey of all adult cardiac transplantation programs in the United States in an attempt to define current practices with regard to LVAD implantation, monitoring panel-reactive antibody (PRA) levels, treatment options, and peritransplantation management. Pretransplantation sensitization with the use of LVAD is a concern to the majority of transplantation professionals and there is no consensus on the need or mode of treatment.

THE USE of left ventricular assist devices (LVAD) as a bridge to transplantation is associated with the development of circulating antibodies.[1] Preformed antibodies increase the risk of allosensitization, hyperacute rejection of the transplanted organ,[2] development of cardiac allograft vasculopathy,[3] and poor graft survival.[4] Several studies have recently investigated preventative measures to decrease the incidence of sensitization[5] more sensitive methods of detecting anti-HLA antibodies,[6] and management strategies for patients who are sensitized.[7,8] Evaluation of humoral sensitization, following ventricular assist device (VAD) placement, is common and is accepted as an important part of pretransplantation assessment. There are currently no available consensus statements or practice guidelines in managing these patients.

Furthermore, a variety of definitions and approaches to sensitization has been described in the literature, but no analyses of actual practice have been reported. We conducted a survey of all adult cardiac transplantation programs in the United States in an attempt to define current practices with regard to LVAD implantation, monitoring panel-reactive antibody (PRA) levels, treatment options, and peritransplantation management.

METHODS

A 22-question survey (Fig 1) was constructed to define perceived clinically significant PRA levels, identify current therapeutic practices, report posttherapeutic monitoring frequency, and define perceived effects of elevated PRA on likelihood of donor crossmatching cardiac allograft survival. The survey was mailed to 1390 clinicians registered in the database of the International Society for Heart and Lung Transplantation (ISHLT) with a prepaid self-addressed business envelope. To identify different individuals from the same program, each program was assigned a number and each survey mailed had a program number written on the form. When discrepant information was received, the majority opinion was counted.

RESULTS

One hundred sixty-seven (12%) surveys were returned, representing 88 programs (69.3% percent of United States adult heart transplantation programs). The proportions of answers to each response to each question are illustrated in Figure 1.

DISCUSSION

Nearly all programs consider a PRA of 10% or greater significant. The type or manufacturer of the device is commonly thought to play a significant role in sensitization, with 93% of people who responded to this survey reporting the Heartmate devices to be most strongly associated with an elevated PRA. Seventy percent of respondents treat elevated PRA, most commonly with intravenous immune globulin and plasmapheresis either alone or in combination. With regard to cardiac allograft vasculopathy, there is nearly a complete consensus that HLA sensitization increases the likelihood of development of vasculopathy. However, regarding the development of acute cellular rejection and decreased graft survival compared with nonbridged patients, 57% of our respondents consider HLA

From the Center for Advanced Heart Failure, Lehigh Valley Health Network, Allentown, Pennsylvania.

Address reprint requests to Dr Ronald Steve Freudenberger, MD, Center for Advanced Heart Failure, 1250 South Cedar Crest Blvd, Allentown, PA 18103.

0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.03.062

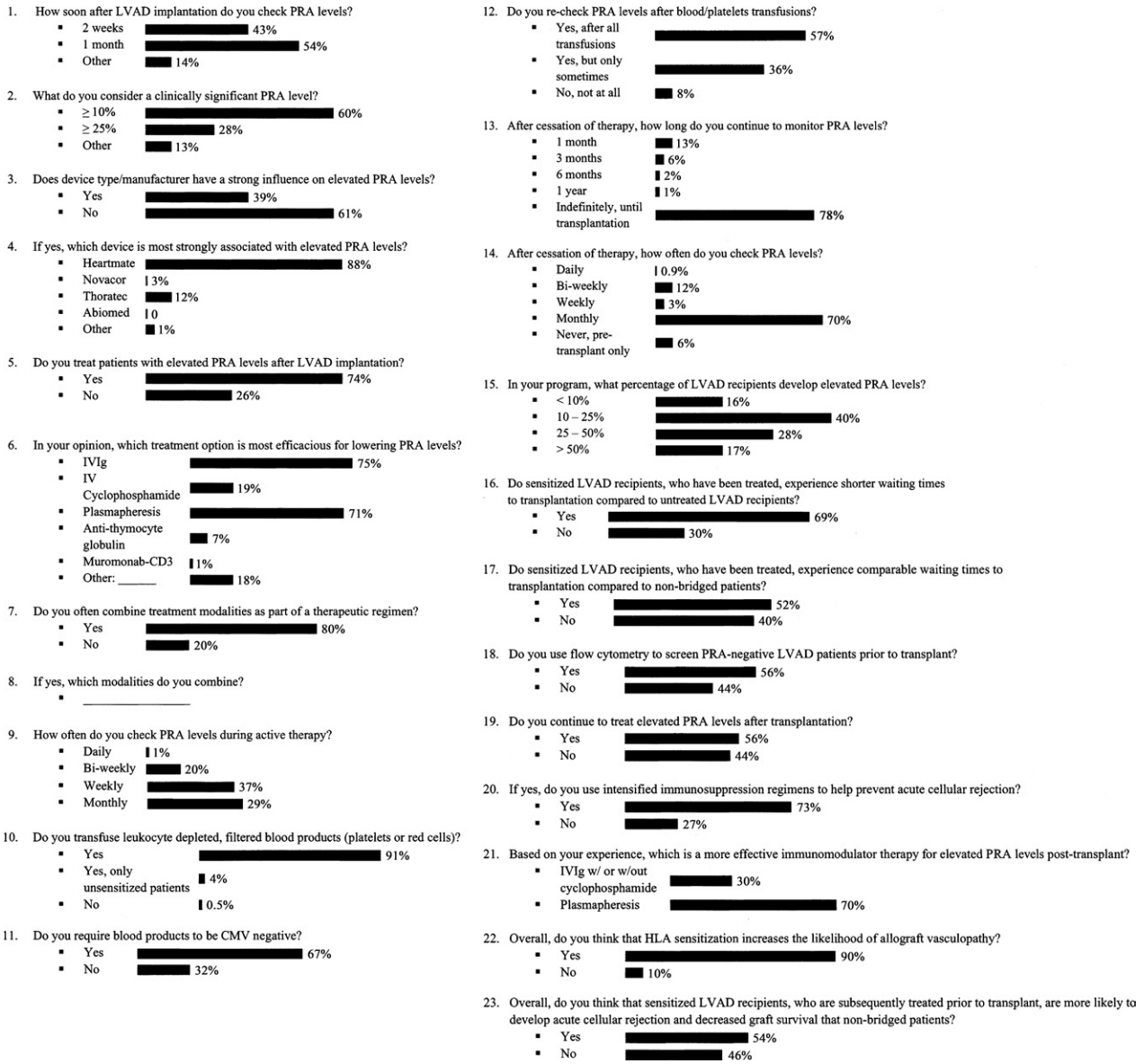

Fig 1. The survey.

sensitization to be a risk factor, whereas 43% do not believe that to be the case.

There are no data in the literature providing information on attitudes and practice patterns of heart transplantation centers. Furthermore, no data exists on outcomes of those treated for high PRA levels versus those not treated. In theory treatment may reduce cellular or humoral rejection but the benefit must be balanced against increased risk of infection. Limited data exist concerning risk factors for development of allosensitization. One center, using Heartmate devices, reported that the only factor that had a significant effect on PRA levels before LVAD was patient's gender (1.3% for men vs 7.4% for women; $P = .005$). During LVAD support, peak PRA levels increased significantly and the gender-associated differences were no longer evident (33.3% men, 34.3% women; not significant). At the time of transplantation, PRAs decreased to 10.9% for men and 7.0% for women (not significant). They also examined the influence of blood products received before transplantation on PRA levels. Patients who received less than the median number of total units (<median) had lower peak PRA values (22.3% vs 49.2%; $P = .01$) and transplantation PRA values (3.5% vs 22.1%; $P = .02$) than those receiving more than the median (>median). When examined by the type of blood product, only the number of platelet transfusions significantly increased the peak PRA (<median, 24% vs >median, 46.9%; $P = .03$). Patients who received blood that was leukocyte-depleted tended to have lower trans-

plantation PRA levels (2.9%) compared with those who did not (13.9%; $P = .18$).[1]

An additional center reported that 17 patients underwent implant surgery with CardioWest C-70 total artificial hearts (TAHs; CardioWest Technologies, Inc., Tucson, Ariz, United States), and 13 with Novacor left ventricular assist systems (LVASs; Baxter Healthcare, Novacor Division, Oakland, Calif, United States) for bridge-to-transplantation at this institution. Two patients died during implantation of the assist devices. Of the remaining 28 patients, 4 (14%) were women (3 with TAHs and 1 with an LVAS). All 4 women (100%) had a positive PRA, whereas only 2 of the 24 men (8%) had positive PRA ($P < .0001$). The transfusion histories of these patients were reviewed. Using chi-squared analysis (alpha = .05), the PRA levels were independent of transfusion of packed red blood cells and fresh frozen plasma. There was an association, however, between platelet transfusions and PRA levels.[9]

A more recent single center report of 54 patients who received leukofiltered cellular blood products (transfused) and 17 patients who received only fresh-frozen plasma (nontransfused) analyzed the impact of leukocyte-filtered cellular blood products on sensitization. Among nontransfused patients, 58.8% (10/17) became sensitized during mechanical support, versus 35.2% of transfused patients (19/54; $P = .15$). There was a trend toward more sensitization during the 12 weeks after device placement in nontransfused patients. Kaplan-Meier analysis revealed significantly more sensitization in nontransfused patients than in transfused patients, despite equal rates of transplantation ($P = .05$). A dose-response analysis revealed significant trends toward less sensitization and lower peak PRA level with more cellular blood product transfusions ($P = .04$). Multivariate Cox regression revealed only increasing transfusions to be associated with a reduced risk of sensitization (hazard ratio .18; $P = .01$).[10]

Thus limited data exist about the true risks and outcomes of patients who are sensitized and there are no data to indicate appropriate treatment and evaluation for this problem.

Limitations include potential selection bias as in all surveys and incomplete response rates. It would be important to know the experience of each respondent with regard to LVAD volume, transplantation volume, and experience with various types of LVAD. However, to increase the rate of response of those surveys we felt that limiting the number of questions and time of answering complex questions was important.

In conclusion, pretransplantation sensitization with the use of LVAD is a concern to a majority of transplantation professionals and is treated in a variety of ways. Studies further defining this problem, its natural history, and treatment are needed. However, in the absence of randomized clinical trials or a large base of historical data, expert opinion remains a basis of clinical practice, and is even recognized by the guidelines as having some value. This survey may, therefore, provide some guidance, although highly imperfect.

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