Editorials

Improving the allograft valve: Does the immune response matter?

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See related article in 2003;126: 232-9.

Can an immunologic attack on cells expressing donor human leukocyte antigens (HLAs) contribute to human allograft valve (AV) deterioration? Not so, say the supporters of a mechanical mechanism of failure.¹ They interpret anti-HLA antibodies in AV recipients²⁻⁴ as irrelevant epiphenomena that result from mechanical failure liberating soluble HLA from the AV to stimulate the immune system.⁵ Unfortunately, this hypothesis is inconsistent with the appearance of anti-HLA antibodies within 30 days of implantation.³ Nevertheless, until recently, a pathogenic role for the immune response in AV degeneration was unproved because a link with functional outcomes was lacking.

The report by Baskett and colleagues⁶ in the July 2003 issue, together with similar conclusions from Dignan and associates,⁷ provides convincing evidence that a significant component of AV degeneration is immunologic. What is the mechanism linking AV deterioration and HLA mismatch between donor and recipient? The same relationship is shown in extensive multicenter studies of solid organ transplants between 0 to 6 antigen HLA mismatches and solid organ graft failure rates.⁸ The accepted underlying mechanism is an allogeneic T-cell response initiated by recognition of nonself HLA-DR on graft dendritic and endothelial cells, followed by an amplification phase against HLA-A and HLA-B molecules in addition to HLA-DR on most parenchymal cells.⁹ Such an immune response causing destruction of HLA-positive cells in the AV provides the most plausible explanation for the observation in the studies by Baskett and colleagues⁶ and Dignan and associates.⁷ Apart from antigen presentation, it is unlikely that the HLA system mediates any nonimmunologic function that could contribute to mechanical AV degeneration. Of interest is a tissue culture study reported by Hoekstra and coworkers¹⁰ predicting that mismatch between HLA-DR on human AV endothelial cells and lymphocytes would produce an allogeneic response potentially capable of damaging the AV.

An HLA mismatch effect is likely to be exaggerated by enhanced AV immunogenicity after shorter incubation times⁷ and in younger recipients who have heightened immune reactivity.^{7,11,12} Younger age is a very important determinant of decreased durability of the aortic AV used for aortic valve replacement.¹² The 10-year actuarial freedom from reoperation for structural degeneration in the 20 years and younger age group at implantation was 47% compared with 93%, 95%, and 96% in those aged 21 to 40, 41 to 60, and more than 60 years, respectively.¹²

Looking for an HLA mismatch effect is inherently difficult because a paired donor and recipient will by chance have few of the 6 possible antigens in common. HLA-A and HLA-B are extremely polymorphic, and even the HLA-DR group consists of 16 discrete antigens.¹³ There have been 2 studies of similar design to that of Baskett and colleagues⁶ that fail to show a significant effect of HLA mismatch on

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AV longevity.^{14,15} Relatively short periods of observation, longer incubation times after harvest reducing AV immunogenicity, small numbers in one study, and older recipient cohorts are likely to have biased toward a negative result. More studies of similar design to that of Baskett and colleagues focusing on younger and larger recipient cohorts, fresher AVs, and longer mean periods of 5 to 10 years' surveillance are needed.

There is widespread interest in reducing the recipient's response to donor HLA in the hope that this will delay AV deterioration, particularly in young adults and children. There are no clinical data to suggest that immune suppression protects the AV from immunologic injury. Ideally, regimens such as low-dose cyclosporine¹⁶ given to protect the right-sided allograft after a Ross procedure should be subjected to trial. It is unlikely there exists enough enthusiasm for such trials in young cohorts because of the potential toxicities of the current antiproliferative, cytotoxic, and calcineurin-inhibiting agents. Animal studies are not promising, suggesting that the AV might be protected from immune destruction only for as long as combination immune suppression is continued (unpublished data).¹⁷

Could an immune response to the AV be minimized by using organ-sharing networks to direct HLA and ABO-typed AV in tissue banks to the best-matched recipient? Although this strategy is highly successful and economically sound for renal allografts, consideration of the size of the AV pool required, donor availability, standardization of AV preparation, and the costs of typing, harvesting, and transport would have to be balanced against the benefits of reduced reoperation rates in a younger population in which the AV is the preferred replacement.

Modification of the AV to reduce immunogenicity is an exciting and evolving area. The pivotal question underlying this endeavor is the nature of the AV cells that display HLA-DR so provocatively to the recipients' T cells. Dendritic cells, also known as "professional" antigen-presenting cells are the most effective exponents of alloantigen presentation.¹⁸ Endothelial cells, also constitutively expressing HLA-DR, might carry out similar functions under the special conditions of cell culture or once exposed to inflammatory cytokines.¹⁰ Thus far, searches of the human aortic valve have found few dendritic cells, but the vascular subpopulation of dendritic cells might not express the expected surface antigens.¹⁹ Modifications of the AV designed to deplete antigen-presenting cells might also damage stromal cells and fibroblasts, with adverse effects on function.

Much research with some clinical application has been directed to tissue-engineered valves. In the hope of avoiding the immune response, decellularized AVs (both aortic and pulmonary) have been clinically implanted. Elkins and colleagues²⁰ have reported 2 years' clinical experience with right-sided implants using AVs treated with the SynerGraft

antigen reduction process (Cryolife Inc, Kennesaw, Ga) to encourage recellularization in vivo. An alternative direction used seeding of a decellularized pulmonary AV in vitro with autologous adult endothelial cells before implantation.²¹

Early promising results from these pioneering studies provide some hope that we might not have to resort to HLA matching or immune suppression. The immune system might not prove easy to bypass, however. The low incidence of anti-HLA antibodies reported by Elkins and associates²² in recipients of decellularized AVs is reassuring but nevertheless raises a note of caution because these antibodies might not be a sensitive marker for the alloreactive cells that are likely to be the actual agents of AV cell injury.³

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