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Evolving Areas in Heart Transplantation

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ABSTRACT

It has been 50 years since Dr. Christiaan Barnard performed the first human-to-human heart transplant in December 1967 in South Africa. Remarkable progress has been made since that time, including changes in surgical techniques, immunosuppression, donor and recipient selection, and post-transplant care. In this paper, we provide a perspective on the changing face of heart transplantation and highlight key evolving areas. Topics that are covered include advances in immunosuppression, screening for acute and chronic rejection, cardiac allograft vasculopathy, and ongoing advancements in cardiac replacement therapy, including xenotransplantation, stem-cell research, tissue engineering, and the total artificial heart. (J Am Coll Cardiol HF 2017;5:869–78) © 2017 by the American College of Cardiology Foundation.

This month marks the 50th anniversary since the first human-to-human heart transplant was performed by Dr. Christiaan Barnard in South Africa in December 1967. Although a groundbreaking moment in history for cardiovascular medicine, this did not come as a surprise to the medical and research community, as the groundwork had been laid since the early 1900s. In celebration of this anniversary, we offer the second part of a 2-part series that discusses advances in immunosuppression and evolving areas of complementary and alternative therapies in the future of cardiac transplantation (**Central Illustration**).

NOVEL IMMUNOSUPPRESSION

In transplant biology, immunosuppression is primarily targeted against the adaptive immune system, which involves both T and B cells. Many novel potential therapeutic targets exist (**Table 1**), but have not been prospectively studied in the cardiac transplant population. Belatacept is a fusion protein composed of the Fc fragment of a human immunoglobulin (Ig) G1 linked to the extracellular domain of CTLA-4, which blocks T-cell costimulation. It has been studied in a randomized controlled trial (RCT) in renal transplant recipients in 2 different doses compared with cyclosporine (CSA). At 12 months, survival was similar between the groups. The belatacept groups had higher glomerular filtration rates, but more episodes of rejection, post-transplant lymphoproliferative disorder, and tuberculosis infection. Belatacept is currently approved for calcineurin inhibitor (CNI)-free regimens in the renal population (1).

The Janus kinase-signal transducer and activator of transcription signaling pathway is important for immune activation. Tofacitinib is the first inhibitor of Janus kinase that is currently approved for treatment of rheumatoid arthritis. It has been compared with tacrolimus in the renal transplant population and found to be equally effective (2). Compared with CSA, tofacitinib was associated with improved renal function, but also with a higher risk of infection and post-transplant lymphoproliferative disorder (3). Sotrastaurin is an agent that blocks early T-cell activation through inhibition of protein kinase C. It has been studied in both preclinical (rat) cardiac transplant models and renal transplant patients and was found to prolong graft survival. However, higher rates of rejection in a CNI-free regimen were observed (4).

Tocilizumab (Actemra, Genentech, South San Francisco, California) is a humanized monoclonal antibody against the interleukin-6 receptor that is currently approved for refractory inflammatory diseases. In preclinical animal models, it reduces allograft rejection, expands T-regulatory cell population, and reduces memory B-cell response. In highly-sensitized renal transplant recipients, tocilizumab reduces

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ABBREVIATIONS AND ACRONYMS

ACR = acute cellular rejection

AMR = antibody-mediated rejection

CMR = cardiac magnetic resonance

CNI = calcineurin inhibitor

CSA = cyclosporine

EMB = endomyocardial biopsy

IgG = immunoglobulin G

LGE = late gadolinium enhancement

alloantibody levels (5). Eculizumab, a humanized immunoglobulin G2/4 monoclonal antibody that inhibits complement by binding to complement component C5, could also be beneficial in antibody-mediated rejection (AMR). It reduced the incidence and severity of AMR in renal and lung transplant recipients (6,7); however, eculizumab has not been studied in heart transplantation, and cost will likely be a barrier to widespread use.

Last, an enzyme from streptococcus pyogenes, IdeS, is a unique agent that cleaves human IgG antibodies. In highly-sensitized renal transplant patients, it has been shown to be effective in reducing alloantibody levels (8), with 2 further ongoing phase 2 clinical trials (NCT02790437 and NCT02426684). These agents all have the potential to be utilized in cardiac transplant recipients, and the field awaits studies in this population and potential future application.

SCREENING FOR ACUTE AND CHRONIC REJECTION

Early detection of cardiac allograft rejection is crucial for post-transplant care. Despite progress in immunosuppression, acute cellular rejection (ACR) and AMR remain serious complications during and after the first post-transplant year. Patients with early treated rejection are at higher risk of late morbidity and mortality (9). The current gold standard for diagnosis is endomyocardial biopsy (EMB), although this is not ideal due to invasive risk, sampling error, and inter-reader variability. Despite decades of basic and clinical research, biomarkers and imaging have been limited in their ability to diagnose and monitor treatment of rejection. Therefore, there is currently an unmet need to create an objective diagnostic test for cardiac allograft rejection.

NONINVASIVE IMAGING. Transthoracic echocardiography is a useful tool to monitor hemodynamically-significant rejection given wide availability and low cost. Disadvantages include operator dependence and inter-reader variability. Many studies have examined systolic and diastolic predictive indexes of ACR (10). Although no single parameter can reliably diagnose rejection, if 1 or more parameters is abnormal, the probability of ACR is higher. Three-dimensional echocardiography can provide more accurate and reproducible measures of ventricular size and function, but is not widely available. Global longitudinal strain has been shown to be a predictor of subclinical rejection (11). Studies of tissue Doppler parameters, such as peak systolic and diastolic wall motion velocity, have yielded mixed results in predicting ACR.

Quantitative contrast myocardial perfusion echocardiography is a technique that can provide both structural and functional parameters and assess the microvasculature. In a murine model of heart transplantation, contrast-enhanced echocardiography demonstrated a decline in microvascular perfusion in mice that developed acute or chronic rejection (**Figure 1**). Notably, myocardial perfusion was restored following immunosuppressive therapy (12). A proof-of-concept study is currently underway to assess the efficacy of contrast-enhanced ultrasonography in detecting heart transplant rejection in humans (NCT02300870).

Nuclear imaging techniques have been studied as a means for noninvasive screening of acute rejection. ^{18F}Fluorodeoxyglucose positron emission tomography imaging has been demonstrated to detect allograft rejection in a murine transplant model (13). Challenges in human transplantation include the required protocol to suppress normal myocyte glucose consumption by a high-fat carbohydrate diet, and confounding diagnoses such as infection and malignancy. Many other agents that target cellular-specific components have been examined in preclinical models, including ^{111}indium-labeled antibody to myosin, ^{99m}technetium-labeled annexin-V, and ^{111}indium labeled oligonucleotides that recognize interleukin-2—all markers that are overexpressed in acute rejection (14,15). None of these agents, however, has been evaluated in large-scale human studies, and thus, the clinical translation is not yet known.

Cardiac magnetic resonance (CMR) imaging is a promising screening modality for detection of rejection. CMR lacks ionizing radiation and can survey the entire myocardium, decreasing the possibility of false negatives due to sampling error as observed in EMB. T2-weighted imaging has been most widely used, as T2 values prolong with higher water content, which increases in edema and inflammation (16). In a study evaluating the diagnostic accuracy of CMR versus EMB for acute rejection, CMR had a high sensitivity (93%) and high negative predictive value (98%), highlighting that CMR could be utilized as a screening test before routine EMB (17). The presence of late gadolinium enhancement (LGE) has also been investigated in small cohorts (18), but the role in transplant screening is not clear in the absence of prospective data with larger sample sizes from multiple centers. Investigational contrast agents are also being developed to improve the sensitivity for detection of inflammation. Ultrasmall