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NHLBI's Program for VAD Therapy for Moderately Advanced Heart Failure: The REVIVE-IT Pilot Trial

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Abstract

Background—VADs are used to bridge heart failure patients to transplantation, to allow their own hearts to recover, or as permanent ("destination") therapy. To date, the use of VADs has been limited to late-stage heart failure patients because of the associated device risks. In 2008, an NHLBI working group met to evaluate the treatment of heart failure using VADs and to advise the institute on how therapy for heart failure may be best advanced by clinical trials involving the devices.

Discussion and Recommendations—Recognizing the improvements in VAD technology and in patient care and selection over the past decade, the working group recommended that a trial be performed to assess the use of chronic VAD therapy in patients who are less ill than those currently eligible for destination therapy. The hypothesis proposed for the trial is that VAD therapy may improve both survival and quality of life in moderately advanced heart failure patients who are neither inotrope-dependent nor exercise-intolerant and have not yet developed serious consequences such as malnourishment, end-organ damage, and immobility. Based on the group's recommendations, NHLBI issued an RFP in 2009 for the REVIVE-IT Pilot Trail which will serve to test the hypothesis and inform the pivotal trial.

Introduction

Over the past 20 years, ventricular assist devices (VADs) have become a standard therapeutic option for treating late-stage heart failure patients. However, their use has increased dramatically during the past few years as a result of improved clinical results realized through superior devices and patient care. With the evolution of the therapy, other potential clinical applications of VADs beyond late-stage heart failure could be considered. With this in mind, the National Heart, Lung, and Blood Institute (NHLBI) convened a working group of experts on heart failure cardiology, cardiac surgery, clinical trial design, medical ethics, and regulatory affairs on March 27–28, 2008 in Crystal City, Virginia. The purpose of the working group was to advise the NHLBI on the treatment of advanced heart

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failure using VADs and how therapy for heart failure may be best advanced by clinical trials involving VADs.

The specific objectives of the meeting were to: (1) assess the current state of clinical utility of VADs; (2) identify near and long-term opportunities for clinical research on VADs and essential components of any identified trials; and (3) make specific prioritized and implementable recommendations for future clinical research involving VADs to help advance public health. This paper constitutes the consensus recommendations of the working group and a description of the request for proposals (RFP) issued by the NHLBI for the pilot trial based on those recommendations. While various recommendations for the trial are provided in this paper and the RFP, the specific protocol and study design for the trial will be based on responses to the RFP.

The clinical research recommended by the working group is expected to address three specific challenges given in the 2007 NHLBI Strategic Plan (see http://www.nhlbi.nih.gov/about/strategicplan/documents/StrategicPlan_Appendix.pdf).(1) They are: (1) to enhance the evidence available to guide the practice of medicine, and improve public health (Challenge 2.4); (2) to accelerate the translation of basic research findings into clinical studies and trials and to promote the translation of clinical research findings back to the laboratory (Challenge 2.1); and (3) to discover biomarkers that differentiate clinically relevant disease subtypes and that identify new molecular targets for application to prevention and diagnosis—including imaging, and therapy (Challenge 1.2).

Background

VADs are currently used to bridge patients to heart transplantation, to allow their own hearts to recover, or as permanent (“destination”) therapy. Using VADs to bridge to heart transplantation is inherently limited by the number of donor hearts available and VAD-assisted cardiac recovery occurs in only a very limited number of cases. Due to associated device risks, destination therapy has been limited in the U.S. to those advanced heart failure patients who are not transplant eligible, have less than two years of life expectancy, and are on maximal heart failure medication. However, outcomes of destination therapy patients have improved substantially since the time when the efficacy of destination therapy was demonstrated through the NHLBI-sponsored REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial.(2) This progress is evidenced through post-approval clinical data from patients receiving devices for destination therapy including that from the NHLBI-sponsored Interagency Registry for Mechanically Assisted Circulation (INTERMACS).(3) A large majority of existing clinical data is based on earlier generation pulsatile VADs. With the advent of the current generation of smaller, continuous-flow VADs such as Thoratec’s HeartMate II® LVAS, survival, risks of serious adverse events, and quality of life are expected to be better than that found in earlier generation pulsatile VADs.

Discussion and Recommendations

Recognizing the improvements in VAD technology and in patient care and selection, the working group considered the highest priority trial to be one to assess the use of chronic VAD therapy in patients who are less ill than those currently eligible for destination therapy. The general hypothesis is that advancing VAD therapy may improve both survival and quality of life in those advanced heart failure patients who are neither inotrope-dependent nor exercise-intolerant and have not yet developed serious consequences such as malnourishment, end-organ damage, and immobility. The working group focused their discussions of the potential trial on critical issues such as patient characteristics, anticipated

survival and expected treatment effects, results of trials involving similar patient populations, equipoise, device characteristics and costs, results of recent VAD trials, risk factors, competing therapies, and regulatory issues.

The working group reached consensus that:

1. an unmet clinical need currently exists for heart failure patients who remain symptomatic with a depressed ejection fraction despite conventional medical therapy;
2. equipoise exists for designing a clinical trial with circulatory assist devices in less-ill patients with the current generation of VADs, and
3. a scientifically rigorous trial design can be designed to address the clinical use of ventricular assist devices in less-ill patients.

The working group also provided the following recommendations concerning the patient population and design for the trial.

Patient Population

The working group recommended that the patients for the trial be those who can benefit from a VAD that will safely improve quality of life and functional capacity and reduce hospitalizations and mortality. This “less-ill” patient cohort should have significant functional impairment and event rates so that the hypothesis that VADs improve outcomes can be tested definitively in an intent-to-treat design study with adequate power. Choosing the patient population for inclusion in such a trial will require careful examination of the risk/benefit ratio for the available appropriate devices. Patients should be expected to be ill enough to potentially benefit from the therapy without undue risk. The estimated mortality rate for this group should be no less than 30% at one year. Identified inclusion criteria include hospitalization in past 6 months, NYHA IIIb or IV, maximal evidence-based therapies for 3 months, duration of heart failure of at least a year, and not on inotropic support within 30 days prior to enrollment.

Trial Design

The working group recommended that the trial be a randomized controlled trial consisting of VAD and optimal medical management (OMM) arms. It would be reasonable to have a 1:1 randomization ratio between OMM and VAD therapy and to include an initial pilot phase followed by a larger definitive phase. The initial phase would be designed to assess feasibility of enrollment and to refine the target population, endpoints, and definitions for the pivotal trial. An initial estimate of the total number of patients needed to adequately power the pivotal trial is 250–300.

A composite primary endpoint of survival and functional status was recommended where the improvement in functional status would need to be substantial and assessed through objective metrics. Survival would need to be at least as good as that in the control group. Secondary endpoints would be hospitalizations, complications, and quality-of-life metrics.

While specific VADs for the trial were not identified, there was a strong consensus within the working group that equipoise for a trial in less-sick patients exists because of recent developments in technology that has resulted in smaller, more reliable, rotary VADs that have fewer mechanical complications than earlier generations of VADs. Device requirements for the trial would need to be defined and any VAD would need to be qualified for the trial based on those requirements. The working group recommended that the trial be

conducted at leading centers by surgeons who have performed a least 12 implants of the VAD to be used at the center for the trial.

The working group indicated that NHLBI should take a leadership role in the design and oversight of the trial. Such NHLBI involvement would (1) provide desired objectivity to the trial design and administration and (2) enhance access to shared data which will help to advance the field.

The REVIVE-IT Pilot Trial—In February, 2009, the NHLBI director approved funding for an NHLBI initiative to conduct a pilot trial to explore the potential benefit of destination therapy using VADs in advanced HF patients who have significant functional impairment but have not yet developed serious consequences such as malnourishment, end-organ damage, and immobility. The initiative was substantially based on the recommendations given above by the NHLBI Working Group on Clinical Use of Ventricular Assist Devices.

The initiative became known as the Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT) Pilot Trial and a Request for Proposals (RFP) for the trial was issued by NHLBI on July 31, 2009. The REVIVE-IT RFP can be found at https://www.fbo.gov/index?s=opportunity&mode=form&id=171de254b47df97fccc1cadcb51f908a&tab=core&_cview=0&cck=1&au=&ck. The REVIVE-IT pilot trial will serve to inform a pivotal trial directed at a large and growing patient population for whom VADs could offer substantial benefit beyond current medical therapies. The intent of both the pilot trial and pivotal trial is to test and advance a therapeutic strategy rather than any specific device. Proposals for the REVIVE-IT pilot trial were due to NHLBI on December 9, 2009. An award is expected to be made by September, 2010 and enrollment of patients is expected to start by June, 2011.

The REVIVE-IT RFP was issued to seek proposals from qualified organizations with the ability to serve as a Data and Clinical Coordinating Center (DCCC) for the REVIVE-IT pilot trial. The DCCC will have the overall responsibility for the operation of the trial and will provide the necessary administrative guidance, oversight, and support to achieve the trial's objectives. In addition to the DCCC and clinical sites, the pilot trial will involve core laboratories, executive and steering committees, an NHLBI-appointed Data and Safety Monitoring Board, and NHLBI program staff. Specific details, such as the requirements for clinical sites and devices to be used in the trial, can be found in the RFP.

The specific hypothesis of the REVIVE-IT pilot trial is that VAD therapy will improve functional status at 12 months post-randomization and all-cause mortality will be no worse than that in the optimal medical management (OMM) arm of the trial. The trial will randomize patients between VAD and OMM arms of the trial. A substantial challenge for the trial is identifying the appropriate HF patients so that the trial can adequately recruit and appropriately test the hypothesis. As recommended by the Working Group, the patient population for the trial is expected to have a minimum mortality of approximately 30% at one year and substantially compromised functional capacity and quality of life. Suggested inclusion criteria include a peak VO2 which is 45–65% of predicted peak VO2, NYHA Class IV or Advanced Class III, HF for at least one year, and an LVEF<35%. However, to insure that HF is not too advanced in the patients, the RFP suggests specific criteria for excluding patients. Recommended exclusion criteria include inotropic therapy within six months prior to randomization and evidence of malnourishment, end-organ damage, or immobility. Due to the nature of the trial, dual or composite primary endpoints involving mortality and functional capacity will be used. A variety of secondary endpoints will be used and are expected to include quality of life, incidence of serious adverse events, device repair and replacement, and cost and cost effectiveness. NHLBI anticipates that the pilot trial will

involve a minimum follow-up of two years involving approximately 100 patients at an estimated 10 clinical sites.

Recent clinical results involving patients supported by smaller, more reliable, continuous flow VADs provide justification for conducting the REVIVE-IT pilot trial now. The latest clinical trial and INTERMACS registry data reveal that VADs from this latest generation of devices provide improved clinical performance over previous generations of VADs(3⁻5). The results seem to be so substantially better that these newer devices appear to be well-positioned for the proposed trial.

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