Introduction

Nearly five million Americans suffer from heart failure, with 550,000 new cases diagnosed with this disease each year. Heart failure is responsible for 11 million office visits and over 3.5 million hospitalizations per year in the US, with a total bill of US$23 billion spent annually on treatment. About 250,000 people in the US suffer from severe, end-stage heart failure (NYHA Class IV). For this patient population, annual mortality on medical therapy approaches 50%, and heart transplantation is often the only treatment option. However, limited donor availability has resulted in only 2,400 transplants per year in the US, with about 4,000 patients populating the heart transplant waiting list at any given time. It is estimated that up to 50,000 patients per year in the US could benefit from heart transplantation if organs were available.

Implantable, wearable left ventricular assist devices (LVADs) have emerged in the past decade as safe and effective treatment measures, improving survival and quality of life, for patients with end-stage heart failure awaiting heart transplantation. The implantable LVAD, which includes pulsatile devices as well as axial flow pumps, allows the patient greater mobility compared with external pumps and longer-term support. The typical, implantable LVAD comprises three primary components: a pump, which receives blood through an inflow cannula and outputs blood through an outflow cannula; a drive console, which powers the pump and features system controls to adjust its operation; and a power source, which typically involves a combination option of direct electricity and a rechargeable battery pack. Despite the implantable feature of these devices, all current US Food and Drug Administration (FDA)-approved LVADs feature external power sources requiring percutaneous driveline connections. A number of fully implantable systems are under development that will eliminate the need for the percutaneous driveline connection in the future and feature implantable and external coils that transfer energy through the skin.

The Novacor® LVAS (WorldHeart Corporation) is an electrically powered, pulsatile flow LVAD with more than 20 years of clinical use, and the first ventricular assist device to provide more than four years of continuous circulatory support without pump replacement. To date, more than 1,500 patients have been supported with the Novacor LVAS, with almost 600 patient-years of experience, and no deaths attributable to device failure. Twenty-five patients have been supported close to, or over, three years on a single device with the Novacor LVAS. Furthermore, a heart failure patient in Italy has been supported for over six years with the Novacor device (elective replacement of the initial device after four years) before successfully receiving a heart transplant.

Device Description

The Novacor LVAS is a fully autonomous system capable of supporting the entire circulation and substantially unloading the left ventricle. The implanted pump drive unit is an integrated pulsatile pump with an electromagnetic driver (solenoid) coupled via springs to the pusher plates of the blood pump. The cyclical, high pulsatile flow mimics the natural function of the heart and takes over the function of the left ventricle. Internal sensors allow the system to recognize native LV function and pump timing. Bioprosthetic valves at the pump inlet and outlet maintain forward flow through a seamless polyurethane blood sac. An external controller provides electrical energy via the percutaneous lead to actuate the driver during the eject cycle. A pair of portable, wearable batteries or an LVAS monitor provides power.

Bridge-to-Transplant Experience

‘Bridging to transplant’ with an LVAD has become a standard of care for patients with end-stage heart failure who continue to decompensate on optimal medical therapy. The number of bridge-to-transplant LVAD implants have increased over the years due to the widening gap between the number of potential cardiac transplant recipients and the number of available donor organs. Between March 1996 and June 1998, a total of 191 patients were enrolled in the Novacor LVAS Bridge-to-Transplantation INTREPID Trial (156 device and 35 control). Implant duration ranged from one to 657 days with mean support duration being 80 days. Survival to transplantation was a remarkable 78%. Therefore, in November 1998, the FDA approved the Novacor LVAS for bridge-to-cardiac transplantation. There are three...
other commercially-available devices approved by the FDA for this indication. These include HeartMate® LVAD (Thoratec Corporation), Thoratec LVAD and the CardioWest total artificial heart.

Textured surface LVADs, such as the HeartMate® device, have demonstrated procoagulant properties with sustained thrombin generation and fibrinolysis.6,10 Additionally, inflammatory cells present on the LVAD surface appear to trigger immunologic sensitization through the production of proinflammatory cytokines leading to T-cell apoptosis and B-cell hyper-reactivity.6 It has been hypothesized that certain cells that adhere to the LVAD surface become activated and selectively absorb circulating hematopoietic precursor and monocytic cells, thereby creating a sustained prothrombotic and proinflammatory environment.4,10 This allosensitization can increase the risk of serious infection, waiting time to transplantation, and rate of post-transplant rejection.9

These host-device interactions at the blood-device interface have not been demonstrated in patients implanted with the Novacor LVAS. In review of a 15-year experience with the Novacor LVAS at New York University, Mount Sinai Hospital, the device was not associated with allosensitization and the rejection profile was similar in Novacor LVAS recipients and a large cohort of non-VAD patients, with a comparable bridge-to-transplant survival.11

**Destination Therapy**

Thoratec’s Heartmate Snap VE was the first device to obtain FDA approval for destination therapy in November 2002. This approval was based on results of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, a 21-site randomized trial in 129 patients that demonstrated that long-term LVAD implantation doubled one-year survival compared with optimal medical management (52% versus 25% respectively) in patients with end-stage heart failure.1 Two-year survival also favored LVAD use (23% versus 8% for the control group). The median survival was 408 days for the LVAD patients and 150 days for medical therapy patients. Infection, cerebrovascular events, and device failure were the three main complications that impeded survival. These complications were predominantly seen in the first 30 days after device implantation. Over 70% of the patients improved to NYHA Class I or Class II after 12 months of support. The Center for Medicare and Medicaid Services has now approved the use of LVAD destination therapy in selected patients with end-stage heart failure who are not candidates for cardiac transplantation. What is not known is whether there are differences between the devices when applied as destination therapy.

In February 2004, the FDA approved a landmark device-versus-device clinical trial to compare the safety and effectiveness of the Novacor LVAS with the HeartMate XVE LVAD in the non-transplant end-stage heart failure population. The Randomized Evaluation of Novacor LVAS In A Non-Transplant population (RELIANT) Trial is a multi-center, randomized clinical trial. It is designed to look at differences between the two devices in transplant ineligible, end-stage heart failure patients who have been treated with optimal medical therapy for 60 of the past 90 days, and who have a life expectancy of less than two years. Statistical design is a 2:1 randomization of the Novacor LVAS to the HeartMate XVE LVAD.

**Reliability**

The number of long-term (> three months) LVAD implantations is increasing because of improved technology, increased availability, increased waiting times for transplantation, and increasingly informed patients.12 Therefore, reliability issues are of critical importance in device-treated patients. Device failure can have minor consequences such as recurrence of heart failure symptoms, or lead to serious adverse events including death. In vitro reliability testing of the Novacor LVAS has demonstrated ≥99.9% reliability at one year, 98.3% at two years, and 85.9% at three years, respectively. On the other hand, probability of failure of the HeartMate device in the REMATCH Trial was 35% at two years, with the device needing replacement in 10 patients and device failure being responsible for seven deaths.1 Further, the seven deaths occurred in a cohort of only 22 patients who were ‘at risk’ beyond 12 months of support duration.13

In more than 1,500 implants of the Novacor LVAS, there have been no deaths attributed to device failure. Lessons learned from observed adverse events during clinical usage of the Novacor LVAS have led investigators to modify and improve the device on an on-going basis, thus optimizing reliability. The reliability of the Novacor LVAS and the Heartmate LVAD will be compared in the RELIANT trial. To date, wear of the main pump bearing represents the only long-term failure in the Novacor LVAS. This bearing wear is detectable by non-invasive device parameter interrogation and tracking, which allows for proactive elective device replacement or priority transplantation.14 Other device-related complications include infection and cerebro-vascular events. The incidence of serious driveline or pocket infections and serious infections of the pump housing inflow or outflow valves can be improved with aggressive infection control protocols. In the REMATCH trial with the Heartmate LVAD, infection of drive line tract or pocket was 0.41 per patient per year. Infection of pump interior, inflow tract or outflow tract was 0.23 per patient per year.1 To date, the experience with Novacor LVAS indicates a device pocket and driveline exit site infection.
risk of 0.013 per patient per year. The risk of cerebrovascular events (ischemic stroke and intracerebral bleed) with the Heartmate LVAD in the REMATCH trial was 15%. Routine anticoagulation was not prescribed for the device-treated patients. The risk of neurologic events has declined steadily with the Novacor LVAS because of design improvements. This risk of embolic cerebro-vascular events with the currently used system is 7.9%. Routine anticoagulation is recommended with a target international normalized ratio (INR) of 3.0–3.5. The RELIANT Trial will compare the incidence of these specific risks between the Heartmate LVAD and the Novacor LVAS.

System Improvements

In an effort to continue clinical excellence and improve recipient quality of life, comfort, and safety, WorldHeart Corporation has recently incorporated several important changes to the LVAS, which include the following system modifications:

• refinements of the blood pump inflow conduit and implementation of a restricted anticoagulation regimen to reduce the incidence of neurological complications that are commonly seen in LVAD patients;17–19
• improved battery power packs to increase support duration and mobility with a 40% decrease in weight over prior versions;
• enhanced cables and connectors to simplify use for easier connect and disconnect, providing improved comfort through lead flexibility, and eliminate inadvertent detachment with positive locking mechanisms;
• a new replaceable percutaneous lead to allow for repair of the lead, due to accidental damage, on an out-patient basis;
• the advanced power pack (battery) charger which is 40% smaller than prior versions, with quieter operation. For reduced maintenance, automated power pack calibration and testing capability has been built in;
• upgraded system software that features downloadable trend displays and a new automatic mode of pump operation that requires less operator interaction;
• a small, quieter charger that is now available for home usage; and
• modifications to the pump/drive unit that provide for quieter pump operation.

Summary

The Novacor LVAS is a reliable, effective electromagnetically-driven left ventricular assist device that improves survival and the quality of life for patients with end-stage heart failure awaiting heart transplantation. With implants in more than 1,500 patients, no deaths have been attributable to device failure, and some recipients have lived with their original pumps for as long as four years. To date, 25 patients have been supported close to or for over three years with the Novacor LVAS, setting industry standards for long-term circulatory support. The Novacor LVAS is commercially approved as a bridge-to-cardiac transplantation in the US and Canada. In the US, the FDA recently approved a pivotal multi-center, randomized clinical trial to expand usage of this device to include transplant ineligible patients for destination therapy. This trial will also compare the Novacor LVAS with the the Heartmate LVAD. Clinical and product research on LVAD technology continues in an effort to develop the ideal left ventricular assist device that is safe, effective and durable.

References

8. Spanier T, Oz M, Levin H, et al., “Activation of coagulation and fibrinolytic pathways in patients with left ventricular assist...