Evaluate Vantage

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AHA 2010 – Hopes for a Natrecor revival dashed by Ascend-HF data

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The American Heart Association (AHA) meeting kicked off today with the presentation of late-breaking clinical trials which could reinvigorate the commercial prospects of two heart failure drugs which once held blockbuster potential: Pfizer's Inspra and Johnson & Johnson's Natrecor.

While the Emphasis-HF study of Inspra turned out to be a rare success for the field, reinforcing the importance of aldosterone antagonists in treating heart failure patients (*Forgotten drug Inspra surprises in mild heart failure, November 15, 2010*), the news from Natrecor's Ascend-HF trial was far less encouraging. Although Natrecor was shown to be safe, alleviating major concerns raised in 2005 which derailed the drug's commercial potential, the data also revealed no significant clinical benefit compared to placebo. Indeed, lead investigators questioned the validity of the FDA's approval of the drug in 2001 and called for clinical outcome trials to be commonplace in all areas of medicine.

Safe, just not particularly effective

Natrecor, known generically as nesiritide, is a vasodilator derived from a naturally-occurring protein, human B-type natriuretic peptide. The drug helps blood vessels to relax, improving circulation and increasing the body's output of excess salt and water.

Acute decompensated heart failure (ADHF) is a major health problem responsible for several millions of hospitalisations per year. Standard therapy has not changed since the 1970s and includes the use of diuretics and vasodilators.

An important and early symptom of ADHF is shortness of breath, or dyspnoea. Uptake of Natrecor following FDA approval was rapid in the belief it had a major effect on dyspnoea. However, a meta-analysis published in 2005 suggested the drug was associated with increased rates of death and kidney failure, after which prescriptions declined just as quickly as they had risen.

The Ascend-HF trial was therefore one of two clinical outcome studies recommended by an expert panel convened by J&J to review the drug's safety and efficacy.

The first study, Fusion II in 890 patients, reported in 2008 and showed the drug to be safe but provided no evidence of improved survival or decreased hospitalisations over standard of care for outpatients. The study concluded: "Nesiritide should not be given as an intermittent outpatient infusion".

The results of Ascend-HF in over 7,000 patients with ADHF are largely similar. The relative safety of Natrecor was confirmed with no evidence of an increase risk of death or kidney failure. However, this good news was made almost redundant by the lack of any significant improvement in dyspnoea, death from any cause or hospital readmissions.

Although the data pointed to a marginal benefit at all these endpoints with nesiritide, none were statistically significant.

Modest value

Dr Adrian Hernandez, co-investigator in the Ascend-HF trial and associate professor of medicine at Duke University School of Medicine, concluded: "we know that nesiritide can be used safely, but there is no mandate to use it because of its modest effects".

Dr Robert Califf, chair of the study and vice chancellor for clinical research at Duke University School of Medicine, says the data now needs to be presented to clinicians and it will be left up to them to decide if the modest benefit of the drug is worth it.

In terms of what kind of patient, if any, should be treated with Natrecor, the advice of the executive committee

ranges from none to a moderately small number of patients; those with early onset of symptoms that have not yet received diuretics.

However, any use beyond this limited setting seems unlikely, given that the drug “certainly does not have a long term effect on clinical outcomes one way or the other”, according to Dr Califf.

Outcome data

The clinical and regulatory experience with Natrecor provides a classic example of how much change has occurred in the last ten years in assessing a drug’s effectiveness.

FDA approval of Natrecor in 2001 was mainly based on a relatively small trial which Dr Califf believes over-estimated the effect of nesiritide on dyspnoea, partly because the original trial withheld any other therapy for the first three hours. “It was more of a scientific experiment", is Dr Califf’s somewhat damning conclusion.

“Nesiritide was approved based on an old fashioned view that you could explain the effects of drugs based on biological understanding, and the biology of nesiritide is very well known”, says Dr Califf.

Dr Califf believes a drug’s risks and benefits can only be understood by adequate outcome trials, pointing to the current demand for such rigorous data in the diabetic market: “I think all fields need to move to that way of thinking".

Costly missed opportunity

As for J&J, the Ascend-HF result is certainly not the outcome it was hoping for.

Natrecor’s potential was one of the primary drivers behind the company’s $2.4bn acquisition of Scios in 2003. Sales in its first full year on the market exceeded $100m and at the time Scios claimed that with 100,000 patients treated with Natrecor in 2002 alone, the drug was “one of the most successful intravenous cardiovascular drug launches ever”.

A launch which in the end turned out to be a damp squibb.

Trial ID	NCT00475852 (Ascend-HF)