Editorial

Omapatrilat - the story of Overture and Octave

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Abstract

At the American College of Cardiology in March two major trials were presented. The publicity surrounding the two could not have been more different. The LIFE demonstrated clear superiority of losartan-based therapy over atenolol-based therapy for the treatment of hypertension. It was published the same week in the Lancet and received major press coverage all over the world.

The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) study in contrast received a subdued reception, very little publicity and is yet to be published. 5770 NYHA class II–IV heart failure patients (LVEF ≤ 30%, recent heart failure hospital admission) were randomised and uptitrated to either 10 mg BD of Enalapril or 40 mg once a day Omapatrilat. The primary end-point of all cause mortality or heart failure related hospitalisation did not differ significantly: 914/2884 for Enalapril and 914/2886 for Omapatrilat (hazard ratio 0.94, CI’s 0.86–1.03, P = 0.187) [1]. Mortality was also similar: 509 for Enalapril and 477 for Omapatrilat (hazard ratio 0.94, CI’s 0.83–1.07, P = 0.339). Omapatrilat was as good as Enalapril but not better. The worrying trend was however, that angioedema was more common with Omapatrilat; 24 (0.8%) versus 14 cases (0.5%).

The OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) study was also presented at this time. 25,267 hypertensives were randomised to Omapatrilat or enalapril and a difference of approximately 3 mmHg in favour of Omapatrilat was seen. Significantly more cases of angioedema were seen with Omapatrilat, 274 (2.17%) compared to 86 (0.68%) with enalapril. Overall death rates were similar, 0.18% for enalapril and 0.15% for Omapatrilat. All adverse events were similar, 51.0% for Omapatrilat and 50.4% for enalapril. The rates of angioedema were much higher in blacks, 5.54% for Ompatrilat and 1.62% for enalapril and for smokers, 3.93% for Omapatrilat and 0.81% for enalapril. We were left with a drug that was, for heart failure, not superior to an ACE inhibitor already off patent, and, as an anti-hypertensive, with an angioedema rate more than double that of an ACE inhibitor in a large head to head comparison. The medical community will be watching to make sure these data are published in full in the medical literature in a timely fashion, in the order of end-points specified in the protocol and with appropriate emphasis on the logical points of presentation.

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At the American College of Cardiology in Atlanta in March two major trials were presented. The outcomes and publicity surrounding the two could not have been more different. The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) demonstrated clear superiority of losartan-based therapy over atenolol-based therapy for the treatment of hypertension with electrocardiographic evidence of left ventricular hypertrophy in patients with hypertension aged 55–80 years [2]. It was positive for the primary composite end-point (death, myocardial infarction, or stroke) with 508 events occurring in the losartan group (23.8 per 1000 patient-years) and 588 in the atenolol group (27.9 per 1000 patient-years;
relative risk 0.87, 95% CI 0.77–0.98, p=0.021). It also demonstrated significantly better survival in diabetics in a large pre-specified sub-study analysis (in 1195 patients mortality from all causes was 63 and 104 in losartan and atenolol groups, respectively; hazard ratio 0.61 (0.45–0.84), p=0.002) [3]. It was published in the same week as its first presentation as two separate papers in the Lancet and received major press coverage all over the world.

The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) study of Omapatrilat in chronic heart failure in contrast received a subdued reception, received very little publicity from its sponsors and is yet to be published. The difference of course is obvious. One was positive for the sponsor the other was not. As part of our drive to ensure major trial results reach public view [4–6] we here present the available results from Overture and the related study OCTAVE which looked at the safety of the drug Omapatrilat in Hypertension. Omapatrilat is a dual enzyme blocker, inhibiting both the angiotensin converting enzyme and neutral endopeptidase, the enzyme which breaks down vasodilator peptides into inactive fragments, most notably the natriuretic peptides [7]. Omapatrilat is the most developed of the class and has been the source of much optimism regarding both its increased efficacy in reducing blood pressure [8] and its potential for the therapy of chronic heart failure. I have already had cause to predict a difficult future for this drug in the International Journal [9].

The pre-clinical and early clinical results for Omapatrilat were encouraging. In a rat post-infarct model omapatrilat improved post-MI survival, cardiac function and cardiac remodelling; albeit to a similar extent to captopril [10]. The first important heart failure trial was the Impress Trial. There was a suggestive trend in favour of omapatrilat on the combined endpoint of death or admission for worsening heart failure (p=0.052; hazard ratio 0.53 [95% CI 0.27–1.02]) compared to lisinopril and a significant benefit of omapatrilat in the composite of death, admission, or discontinuation of study treatment for worsening heart failure (p=0.035; 0.52 [0.28–0.96]). Omapatrilat improved NYHA class more than lisinopril in patients who had NYHA class III and IV (p=0.035). The primary end-point of exercise tolerance was not superior, however, for Omapatrilat [11].

Major efficacy advantages for anti-hypertensive effect were seen in hypertension compared to standard agents, particularly for the difficult to treat area of isolated systolic hypertension. Bristol-Myers Squibb, the manufacturer and patent holder was clearly impressed. It filed a new drug application with the FDA and the regulatory authorities in the EU in December 1999. In April 2000, BMS voluntarily withdrew the application in response to questions raised by the FDA regarding the comparative incidence and severity of angioedema reported within the submitted database. The share price fell dramatically indicating the importance this drug held for BMS. The issue of angioedema, however, was too worrying for the scientific community, and we needed a clear answer as to whether Omapatrilat was to be bedevilled by an unacceptably high incidence of this potentially serious side-effect. An increased tendency to angioedema could be due to a greater enhancement in bradykinin levels as has been seen in animal models [12] and as would be expected from its mode of action.

In July 2000, BMS reported that it planned to conduct a multinational, 25,000 patient study (OCTAVE – Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) to compare the efficacy and safety of omapatrilat against enalapril in the treatment of hypertension. The purpose was clearly to establish whether the frequency of angioedema was similar to the familiar and very efficacious and accepted ACE inhibitor class. The OCTAVE trial was expected to generate data by mid-2001, which could allow for a launch by early 2002. Analysts BMS would launch the drug in late 2002 or early 2003 and predicted sales of between $585 million and $1.8 billion in 2005 [13]. There was already a major clinical trial programme underway, in hypertension as well as chronic heart failure.

The Omapatrilat in Persons with Enhanced Risk of Atherosclerotic events (OPERA) trial is a large clinical trial of omapatrilat, a vasopeptidase inhibitor, in patients with stage 1 isolated systolic hypertension (ISH). This 5-year multinational, randomized, double-blind, parallel-group, placebo-controlled, forced-titration study planned to recruit 12,600 subjects to determine whether treatment with once-daily omapatrilat (target dose 40 mg) will reduce cardiovascular (CV) morbidity and mortality (primary end point
defined as the composite of fatal/nonfatal stroke, fatal/nonfatal myocardial infarction, fatal/nonfatal heart failure, and other CV mortality) in older (> or = 65 years) men and women with enhanced risk for atherosclerotic events due to stage 1 ISH plus other risk factors. Blood pressure inclusion criteria were systolic blood pressure (SBP) 140 to 159 mm Hg (SBP 125 to 139 mm Hg in diabetic individuals) and diastolic blood pressure (DBP) <90 mm Hg [14]. It was planned well before OCTAVE but was held pending the safety results heralded by OCTAVE.

The OVERTURE study was designed to test whether Omapatrilat offered advantages over the ACE inhibitor class in moderate to severe chronic heart failure. Major advances have been made in the treatment of heart failure [15] but there remained a need for improved treatments [16]. Overture was a study of NYHA class II, III or IV heart failure with left ventricular ejection fraction less than or equal to 30% with a hospital admission within 12 months due to heart failure. Omapatrilat or enalapril was given in addition to standard therapy for heart failure. Patients were randomized and uptitrated to either 10 mg BD of Enalapril or 40 mg once a day of Omapatrilat. The primary end-point was all cause mortality or heart failure related hospitalisation. 5770 patients (79% male) were randomized to either enalapril (2884) or Omapatrilat (2886). The primary end-point did not differ significantly between the two groups: 914/2884 for Enalapril and 914/2886 for Omapatrilat (hazard ratio 0.94, CI’s 0.86–1.03, P = 0.187) [17]. Mortality was similar: 509/2884 for Enalapril and 477/2886 for Omapatrilat (hazard ratio 0.94, CI’s 0.83–1.07, P = 0.339). This showed that Omapatrilat was as good as Enalapril but not better. The worrying trend was however, that angioedema was more common with Omapatrilat; 24 (0.8%) versus 14 cases (0.5%).

Angioedema pre-Octave had been seen at a rate of about 0.5% in non-black takers of Omapatrilat and in 2.1% of black takers. We know relatively little about the frequency of angioedema with the ACE inhibitors. The incidence has stated to vary from 1 to 7 cases per thousand [18] although cases may be missed or delayed [19]. High or rapidly increasing levels of bradykinin have been implicated [20]. OCTAVE was a multi-centre randomized double-blind comparison of Omapatrilat and enalapril in 25,267 hypertensive subjects aged over 18 years with a blood pressure equal to or greater than 140 mmHg systolic and/or 90 mmHg diastolic either on treatment or not. There was a significantly greater reduction in BP with Omapatrilat compared to enalapril (difference approximately 3 mmHg). Overall death rates were similar, 0.18% for enalapril and 0.15% for Omapatrilat. All adverse events were similar, 51.0% for Omapatrilat and 50.4% for enalapril. The worrying finding was, however, that there were significantly more cases of angioedema with Omapatrilat, 274 (2.17%) compared to 86 (0.68%) with enalapril. The rates were much higher in blacks, 5.54% for Omapatrilat and 1.62% for enalapril and for smokers, 3.93% for Omapatrilat and 0.81% for enalapril. We were left with a drug that was, for heart failure, not superior to an ACE inhibitor already off patent, and, as an anti-hypertensive, with an angioedema rate more than double that of an ACE inhibitor in a large head to head comparison. The prospects for Omapatrilat suddenly looked less attractive and the share price of Bristol Myers Squibb dropped approximately one quarter over night. Does this mean the end of this whole class?; it is still too early to say. We will however be watching to make sure these data are published in full in the medical literature in a timely fashion, in the order of end-points specified in the protocol and with appropriate emphasis on the logical points of presentation.

References


