REVIEW ARTICLE

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Optimising Outcomes in End-Stage Heart Failure

Differences in Therapeutic Responses between Diverse Ethnic Groups

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Abstract

Clinical and pathophysiological differences between Japanese and Caucasian patients are observed in many aspects of heart disease. Indeed, data derived from studies in one population cannot be automatically extrapolated to the other. The therapeutic goal of heart failure has recently been aimed at improving mortality in Western societies. The long-term use of an inotropic agent in the energy-starved failing heart has been expected to increase myocardial energy use and accelerate the disease process. However, this may not be the case in the Japanese population in whom mortality is relatively low. Therefore, vesnarinone therapy could be justified, since it allows optimal care in terms of an improved quality of life. Nevertheless, re-analysis of the findings of the Vesnarinone Trial (VEST) emphasised again the reasons for the precautions relating to vesnarinone use: (i) vesnarinone was associated with increased death, usually occurring within 7 months of initiation of the drug; (ii) the mortality rate was higher in patients receiving concomitant digoxin, which necessitated close monitoring of renal function; (iii) the mortality rate also increased in patients with severe bradycardia, indicating the importance of regular ECG monitoring; and (iv) improvements in cardiac function and symptoms by the drug may result in sudden death, particularly in patients with severe heart failure. Such patients should be closely monitored by a physician.

Heart failure is a syndrome rather than a disease. Clinical abnormalities in heart failure are characterised by a limitation in exercise tolerance and a high risk of death.[1] Therefore, in the management of this highly lethal syndrome, much emphasis is now being placed on an improvement in prognosis.[2]

Because a decrease in cardiac contractility constitutes the most important underlying mechanism of this syndrome, intense interest and effort have been directed at developing new cardiotonic agents to enhance contractile function in the failing heart. A number of inotropic agents have been introduced that increase cyclic adenosine monophosphate, either by increasing its synthesis or reducing its degradation. These agents exerted dramatic short-term haemodynamic benefits; however, long-term treatment was associated with an accelerated disease process and an adverse effect on survival.[3] In the midst of scepticism regarding the search for orally effective inotropic agents, a new formulation of the phosphodiesterase inhibitor, vesnarinone, was developed.

1. Clinical Experience with Vesnarinone

Vesnarinone is a quinolinone derivative. In addition to its inhibition of a specific isoform of phosphodiesterase, vesnarinone modifies the action potential, increasing the opening frequency of calcium channels and inhibiting the outward potassium current.[4-6] In the initial multicentre study conducted in Japan, 21% of patients in the placebo group were withdrawn from the study because of death or worsening heart failure during the 3- month

study period, while only 2% of patients treated with vesnarinone 60mg once daily were hospitalised because of worsening congestive symptoms.[7] Subsequently, a survival study of this agent was carried out in the United States.[8] In this study, patients with New York Heart Association (NYHA) class III heart failure and an ejection fraction of 30% or less were randomised to treatment with vesnarinone 60 or 120mg/day, or matching placebo. Although the 120mg arm of the study was terminated prematurely because of a 2-fold increase in mortality, the 60mg arm demonstrated a 62% reduction in mortality over the 26-week study period, compared with the placebo arm. These findings suggested that vesnarinone has a narrow therapeutic range, but has the potential to improve the clinical outcome in patients with severe heart failure.

However, because of the short duration of the trial, the small total number of adverse events and a trend toward an adverse effect on mortality with the higher-dose regimen, another large-scale trial with a longer follow-up period was initiated to confirm the long-term effects of vesnarinone on both mortality and morbidity in patients with reduced left ventricular ejection fraction and symptoms of severe heart failure. The Vesnarinone Trial (VEST) enrolled a total of 3833 patients at 189 study centres; patients were randomised to receive vesnarinone 30 or 60mg, or placebo.[9] After the pre-specified total number of deaths had occurred in the placebo group, the trial was terminated with a mean follow-up time of 286 days. However, contrary to our initial expectation, the results of this trial revealed a dose-dependent excess mortality in the active treatment group, with mortality rates of 22.9% in the vesnarinone 60mg group and 21.0% in the vesnarinone 30mg group, compared with 18.9% in the placebo group. Nevertheless, compared with placebo, vesnarinone significantly improved the cardiothoracic ratio, as determined by chest x-ray.[10]

In addition, significantly greater improvements in quality of life were observed at 8 and 16 weeks in the vesnarinone 60mg group than in the placebo group, although the difference in the degree of improvement between the groups was no longer significant by 26 weeks. Many patients, particularly those in NYHA class IV or those with severe symptoms, died after an improvement in NYHA classification.[10] There was a similar tendency for a dissociation between effects on mortality and quality of life in the Digitalis Investigation Group's study[11] and the Valsartan Heart Failure Trial.[12] In both studies, the mortality rate was unaffected by the active treatment but the combined endpoint of mortality and morbidity was reduced as compared with placebo. In both studies, the treatment tended to be more beneficial in patients at high risk, in patients with low ejection fractions or enlarged hearts, and in patients in NYHA class III or IV, as in the VEST trial.[9] There is a possibility that the increased exercise capacity resulting from treatment may have caused fatal arrhythmias in these critically ill patients. Therefore, these patients should be appropriately monitored by a physician, for example in hospital, during the course of treatment with the drug in order to prevent them exercising excessively.[10] It was reported that, after the data on vesnarinone were released and the increased mortality rate was explained to the patients in the study, many opted to continue the therapy because of the perception that their symptoms had improved.

In the Japanese trial,[7] quality of life was also assessed on the basis of questionnaires on general well-being and on work performance. The degree of change in these variables was greater in patients treated with vesnarinone compared with the placebo-treated patients, although statistical significance was obtained only in the general well-being scale. One patient lost consciousness for 10 minutes after beginning vesnarinone treatment. It was subsequently noted that the patient had premature ventricular contractions; however, there was no evidence of a relationship between the arrhythmia and unconsciousness.[7]

2. Quality of Life as a Primary Goal of Heart Failure Treatment

These results raised serious concerns about the adequacy of endpoints used to evaluate therapeutic efficacy in the treatment of heart failure. It was

pointed out that, for many patients with advanced heart failure refractory to the best available medical therapy, survival is not a goal of therapy unless it is accompanied by some relief of symptoms, and these patients are quite willing to accept a greater risk of death in exchange for the promise of an improved quality of life.[13-17] Even 40% of patients with less severe heart failure (NYHA class II or III) were willing to accept a 5 in 100 or greater risk of drug-induced death for a 5-point improvement in the 105-point score on the Living with Heart Failure (LIhFE) questionnaire.[18] Many clinical trials of chronic heart failure have incorporated the LIhFE questionnaire as a measure of quality of life. On the basis of a correlation between changes observed on the total and physical dimension questionnaire in scores and the changes in exercise capacity, the LIhFE questionnaire was considered to be a reliable and valid patient self-assessment of therapeutic benefit. However, discrepancies in findings between these two parameters were also noted in many individual patients, emphasising the conceptual distinction between objective measures and subjective assessment of disability.[19]

In Japanese trials of heart failure, the Specific Activity Scale (SAS) is often employed as a measure of quality of life.[20] The metabolic costs of various types of physical activity are measured and questionnaires are prepared for specific physical activities that a patient would perform either customarily or sporadically in daily life. A patient is asked to specify whether he/she could perform each type of activity without symptomatic limitation or not. When the questionnaire data are summarised, a given number of metabolic costs (SAS) are derived for each patient with regard to self-perceived exercise tolerance. In 20 patients, two interviewers evaluated the SAS independently. Thereby, interobserver variations in estimating the SAS were substantially reduced. The clear linear correlation observed between the SAS and peak oxygen consumption indicates that the SAS can reliably predict exercise capacity.[20]

A clinical trial conducted in Europe investigating another positive inotropic agent (pimobendan) that enhances myocardial contractility by phosphodiesterase inhibition together with a calciumsensitising effect showed a trend towards a higher mortality rate and combined adverse cardiac outcomes in the active treatment group.[21] These findings again raised concerns regarding the long-term safety of even modest phosphodiesterase inhibition. A similar study of this agent carried out in Japan demonstrated that this drug may favourably modify the prognosis and quality of life, expressed as the SAS score, in patients with chronic heart failure.[22] In this study, during 52 weeks of follow-up in 276 patients, there were only two deaths (one in each group). These data again confirm that, in contrast to the recent pessimism regarding the long-term efficacy of cardiotonic agents, they may be useful in the Japanese population for preventing the worsening of heart failure and improving quality of life without affecting mortality.

3. Vesnarinone as a Potential Cytokine Inhibitor

Elevated circulating levels of cytokines have been noted in patients with heart failure and it has been suggested that immunological responses mediated by cytokines may play an important role in the pathogenesis of heart failure.[23-26] Most cytokines act as local autocrine or paracrine mediators and do not act in an endocrine fashion. Therefore, the systemic elevation of cytokines produces a series of pathological reactions. Serum levels of cytokines correlate with the severity of heart failure, although their net biological effect may be determined primarily by the body compartment in which they are produced and not by the circulating serum levels.[27-29] Proinflammatory cytokines exert a cardiodepressant effect through a variety of mechanisms. When mice were inoculated with the myocardiotropic variant of encephalomyocarditis virus, 75% of animals died during the first 2 weeks. Treatment with vesnarinone started simultaneously with virus inoculation increased the survival rate in a dose-dependent manner.[30] Vesnarinone did not affect the virus titre in the myocardium of the infected animals, nor did it inhibit virus replication in cultured murine myocytes. Furthermore, it did not

directly protect the myocytes from the virus-induced cell injury. Vesnarinone inhibited natural killer (NK) cell activity, which was assessed by incubating effector cells obtained from the spleens of the infected mice with ^{51}Cr-labelled target cells, and by measuring the amount of radioactivity released from the killed targets. This unique action of vesnarinone on NK cells was considered to be related to its inhibitory action on potassium channels, because potassium channels regulate Ca^{2+}-associated signal transduction pathways and play a substantial role in T-cell activation.[31,32]

When stimulated peripheral blood mononuclear cells, human Jurkat T-cell line, and THP-1 monocyte cell lines were inoculated with vesnarinone at concentrations similar to those found in patients treated with this drug, levels of tumour necrosis factor-α (TNFα), interferon-γ. (IFNγ), interleukin (IL)-1β, and IL-2 in the culture supernatants were equally reduced in all cell lines in a dose-dependent manner.[33,34] Therefore, vesnarinone exerts its inhibitory effect on the orchestrated action of a network of cytokines. This effect of disrupting the action of several cytokines simultaneously has a particular advantage over the elimination of a single cytokine from the biological system by targeted gene disruption or neutralisation with antibodies because the bioactivity of cytokines is characterised by their redundancy and pleiotropy.[35] However, such cytokine regulation by vesnarinone has been variable in the clinical setting, depending on the severity of heart failure.[36] Analysis of the cytokine database obtained from 1200 patients enrolled in the VEST trial demonstrated that circulating levels of cytokines and cytokine receptors were elevated in patients with advanced heart failure associated with increased mortality.[37] On the other hand, no measurable anticytokine effects of vesnarinone were observed in this trial.[38]

4. Racial Differences in Cardiovascular Disease and Endpoints of Heart Failure Treatment

Cardiovascular disease may affect different races differently. We assessed epidemiological and pathophysiological differences in cardiovascular diseases across racial groups. The incidence of organic coronary artery disease, a major cause of heart failure in Western societies, is relatively low in Japan. The age-adjusted death rate due to ischaemic heart disease in Japan has been estimated to be one-sixth of that observed in the United States.[39] We compared the post-hospital outcome of acute myocardial infarction in 106 Japanese patients and 789 patients in North America during an average follow-up period of 26 months.[40] Some risk factors more frequent in Japanese patients were older age (61 vs 58 years, $p < 0.001$), a higher percentage of males (88 vs 75%, $p < 0.008$) and cigarette smokers (30 vs 14%, $p < 0.001$). After adjustment for clinical variables and medications, Cox analysis showed a significantly greater risk of experiencing a primary endpoint (cardiac death, nonfatal myocardial infarction or unstable angina) in North American patients. Several extensive clinical trials carried out in Western populations have revealed that newly synthesised, orally active inotropic agents produce a dramatic short-term haemodynamic benefit in patients with advanced heart failure; however, the long-term of these agents is associated with an excess mortality.[41-44] Therefore, all such agents have now been limited to the acute management of severe heart failure and are regarded as unsuitable for long-term heart failure treatment. However, patients enrolled in the heart failure trials in Western populations do not represent typical patients encountered in Japan. Mortality due to heart disease is substantially lower in Japan than in all other Western countries.

Re-analysis of the VEST trial results indicated that the mortality rate was lower in patients not receiving concomitant digoxin. In the Japanese trial,[7] 76% of the active treatment group and 74% of the placebo group received digoxin. Serum digoxin levels are greatly affected by renal function. Therefore, appropriate monitoring of blood urea nitrogen or creatinine levels was recommended on the basis of the re-analysis results.[10] In the Japanese trial, patients with renal dysfunction were excluded from the outset. The re-analysis revealed a reduced

survival rate in patients with severe bradycardia and, specifically, a prolonged R-R interval on ECG; however, the heart rate remained unchanged in the Japanese trial. Vesnarinone treatment was also shown to be associated with a higher annual mortality rate in patients who had higher plasma levels of the major metabolites of vesnarinone (OPC-8230 and OPC-18136) than in those who had not.[10] Metabolite data are not available from the Japanese trial; however, ethnic differences in drug pharmacokinetics may have also been related to the differences in the effects.[45] Under these circumstances, long-term therapy with inotropic agents, and particularly with vesnarinone, may be justified in Japanese heart failure patients with a low mortality rate as optimal care in the context of relief of symptoms and an improved quality of life.

5. Conclusion

Clinical and pathophysiological differences between Japanese and Caucasian patients are observed in many aspects of heart disease. Therefore, data derived from studies in one population cannot be automatically extrapolated to the other. Accordingly, the individual response to a given medication is extremely important, even when it does not match the mean effect of an intervention in a large trial. The therapeutic goal of heart failure has recently been aimed at improving mortality in Western societies. The long-term use of an inotropic agent in the energy-starved failing heart has been expected to increase myocardial energy use and accelerate the disease process. However, this may not be the case in the Japanese population in whom mortality is relatively low. Consequently, vesnarinone is still being marketed in Japan. This therapy could be justified, since it allows optimal care in terms of an improved quality of life. However, re-analysis of the findings of the VEST trial[10] emphasised yet again the reasons for the precautions relating to vesnarinone use, namely: (i) vesnarinone was associated with increased death, usually occurring within 7 months of initiation of the drug; (ii) the mortality rate was higher in patients receiving concomitant digoxin, which necessitated close monitoring of renal function; (iii) the mortality rate also increased in patients with severe bradycardia, indicating the importance of regular ECG monitoring; and (iv) improvements in cardiac function and symptoms by the drugmay result in sudden death, particularly in patients with severe heart failure. Such patients should be closely monitored by a physician.

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