REVIEW ARTICLE

Drug Safety 2004; 27 Suppl. 1: 1-9
0114-5916/03/0001-0001/$30.00/0

© Adis Data Information BV 2004. All rights reserved.

Clinical Characteristics of Vesnarinone

Arthur M. Feldman

Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Abstract

Congestive heart failure is a common condition with a poor prognosis. Its high rates of morbidity and mortality produce a huge societal burden. Current pharmacological treatment approaches are based on angiotensin-converting enzyme inhibitors, diuretics and digoxin, but up to 5% of patients may have refractory disease with persistent symptoms at rest. Such patients with advanced-stage disease may be candidates for treatment with the novel agent vesnarinone, a mixed phosphodiesterase inhibitor and ion-channel modifier that has modest, dose-dependent, positive inotropic activity, but minimal negative chronotropic activity.

Vesnarinone improves ventricular performance most in patients with the worst degree of heart failure. However, before the initiation of vesnarinone therapy, risk–benefit profiles in individual patients should be considered, because in two large-scale studies [i.e. of the high dosage used in the Vesnarinone Study Group Trial (VSGT), and of both dosages used in the Vesnarinone Trial (VEST)] a dose-dependent increase in mortality was identified for vesnarinone 30–120 mg/day. The two studies also found significant vesnarinone-induced, short-term improvements in quality of life (QOL) in patients with refractory end-stage heart failure. Such patients are the most willing to trade-off a slightly increased risk of mortality for improved QOL. It is thus in these patients with refractory end-stage heart failure that vesnarinone may ultimately establish an important treatment role. However, detailed further investigation of the overall place of vesnarinone in heart failure management, with particular reference to the clinical potential of vesnarinone plus β-blocker combination therapy, for example, is certainly warranted.

1. Introduction

Congestive heart failure is associated with enormous and growing socioeconomic impact.[1,2] In the USA, approximately 4 million people have heart failure, with more than 400 000 new cases of the disorder diagnosed each year.[1–4] Among the Medicare population, heart failure is the most common cause of hospitalization and, in 1990, treatment costs for the condition were estimated to exceed $US10 billion.[1,5] The illness is particularly prevalent in elderly individuals.[1] It also has a poor prognosis: annual mortality rates of 15% to more than 50%, depending on disease severity, have been reported.[1,6,7]

The current pharmacological treatment strategy for congestive heart failure is based on the following: angiotensin-converting enzyme (ACE) inhibitors to reduce symptoms, disease progression and mortality; loop diuretics to reduce congestion; digoxin to improve left ventricular function; β-blockers to effect adaptive cardiac remodelling, and spironolactone to improve survival.[1,2,5,7–9] However, many patients receive ACE inhibitors at too low a dosage or are not given these compounds at all, and β-blockers are underutilized.[1,7,10] Diuretics may also be underutilized, in this instance because of physician concern about the potential for electrolyte abnormalities and neurohumoral activation.[1–3,7,10]

Much interest has recently focused on the role of β-blockers (e.g. bisoprolol, carvedilol, metoprolol),

which counter sympathetic nervous system activation, in the management of clinically stable patients with New York Heart Association (NYHA) class II–IV heart failure.[5,7,9–13] Despite initial unease about the possibility of negative inotropic effects, β-blockers significantly reduced symptoms and markedly reduced mortality in patients with chronic heart failure.[5,8,10–12] Importantly, β-blockers significantly decreased heart size and improved heart function.[12]

Although the phosphodiesterase inhibitors amrinone, milrinone and enoximone are no longer widely used in chronic heart failure, because of their well-documented capacity to increase mortality,[2,4,6,7,9,10,14] low doses of the mixed phosphodiesterase inhibitor and ion-channel modifier vesnarinone have considerably improved quality of life (QOL), and even reduced mortality in one study in heart failure patients.[8,9] Further studies are required to define clearly the role of vesnarinone in heart failure; and, of emerging interest, a therapeutic 'niche' may even manifest for β-blockers and phosphodiesterase inhibitors used in combination.[11,15] The purpose of this review, however, is to focus principally on various aspects of the clinical potential of vesnarinone in the management of advanced heart failure.

2. Pharmacodynamic Profile of Vesnarinone

2.1 Mechanisms of Action

Vesnarinone is a quinolinone derivative, whose mechanism of action is multifaceted but incompletely understood.[10] Nevertheless, the drug possesses the following principal experimental effects:[3,4,6,8,10,14,16]

- Weak inhibition of phosphodiesterase type III, which leads to increased myocardial contractility. Despite such dose-dependent, positive inotropic activity,[17] various animal studies indicate that vesnarinone does not increase maximal oxygen consumption in the normal heart, but may reduce this parameter in the ischaemic, failing heart.[3]
- Prolongation of action potential duration. Vesnarinone-induced reductions in the delayed outward and inward-rectifying potassium currents have been reported, as have increases in intracellular sodium and calcium concentrations. The latter increase has been attributed to increased currents through L-type calcium channels.[18,19]
- Minimal negative chronotropic and vasodilatory activity.[17]
- Inhibition of cytokine production.

Vesnarinone has demonstrated improvements in systemic haemodynamics and exercise tolerance in patients with chronic heart failure (see section 2.2).[14] However, the pharmacological effects that specifically explain the clinical activity of vesnarinone in congestive heart failure have yet to be clearly defined.[20] It appears that vesnarinone does not act by reducing neurohumoral activation. In a 6-month study of 21 patients with heart failure and ejection fraction $< 30\%$, vesnarinone 60 mg/day had no statistically significant effects on neurohumoral indices such as plasma renin activity, and levels of atrial natriuretic factor and noradrenaline (norepinephrine).[21]

2.2 Haemodynamic Effects

Few pharmacodynamic studies have evaluated the haemodynamic effects of vesnarinone in patients with heart failure. Nonetheless, in a randomized, single-blind study, in which eight patients with NYHA class II–III chronic, stable congestive heart failure received vesnarinone 60 mg/day or placebo for 4–8 weeks, vesnarinone significantly enhanced left ventricular performance: left ventricular end-systolic dimension was significantly reduced, afterload mismatch was corrected, and the end-systolic pressure–dimension relationship was shifted leftwards with an increased slope.[22]

A randomized, double-blind study evaluated patients with chronic NYHA class II–IV dilated cardiomyopathy treated for 3 months with vesnarinone 30 mg/day ($n = 11$) or 60 mg/day ($n = 10$).[23] Statistically significant haemodynamic changes were noted with the higher vesnarinone dosage. That is, significant increases from baseline

© Adis Data Information BV 2004. All rights reserved.

were recorded in cardiac output (+14%), ejection fraction (+5%) and the ratio of left ventricular maximal power to end-diastolic volume squared (PWR_{max}/EDV^2; +24%), and decreases were observed in end-systolic volume (−6%) and effective arterial elastance (−11%). The positive inotropic effects of the 60 mg/day dosage were attained without a significant decrease in heart rate and were relatively modest. Indeed, the improvement in PWR_{max}/EDV^2, a sensitive and specific indicator of cardiac contractile function, was approximately five times less than that documented after the administration of intravenous dobutamine 10–20 μg/kg per minute to patients with NYHA class III–IV heart failure.[23]

In 6 of 17 patients (35%) with severe heart failure (NYHA class III–IV) and baseline ejection fraction < 30%, vesnarinone 30–60 mg/day administered for 12 months improved the ejection fraction by > 7%.[24] Importantly, markedly more vesnarinone-treated patients with an initial ejection fraction of < 25% versus > 25% experienced a 12-month improvement in this parameter (83% vs 18% of patients). The right ventricular area change improved by 19% in the low ejection fraction group, but remained unchanged in patients with an initially higher ejection fraction. These findings of considerably improved biventricular performance in patients with the greatest impairment of systolic function suggest that vesnarinone may have its optimum therapeutic benefit in the most severe heart failure.[24]

2.3 Effects on Cytokine Production

Several *in vitro* and animal studies have suggested that vesnarinone inhibits the production of cytokines such as tumour necrosis factor alpha (TNFα).[25–29] In lipopolysaccharide-stimulated whole blood from 20 heart failure patients, for example, vesnarinone inhibited the *in vitro* production of TNFα, interferon-γ and interleukins (IL) 1α and 1β.[29] The inhibition of cytokine production has been postulated to contribute to the clinical activity of vesnarinone in heart failure, because TNFα and other cytokines reduce myocardial contractility and encourage the progression of heart failure through direct toxic effects on the myocardium and vasculature.[29,30] Recent *in vivo* results, however, cast doubt on this potential mechanism of vesnarinone effect: in fact, in a 24-week study of >1000 patients with NYHA class III–IV heart failure, vesnarinone 30–60 mg/day did not markedly alter the circulating levels of TNFα, soluble TNF receptors types 1 and 2, IL-6, and soluble IL-6 receptor.[30]

3. Pharmacokinetic Profile of Vesnarinone

Preliminary pharmacokinetic data from 21 healthy male volunteers indicated that the plasma concentrations of vesnarinone attained were proportional to the single, oral doses administered; that is, across the dose range 7.5–240mg.[31] After the administration of a 60mg vesnarinone dose to a total of 33 healthy male volunteers, the following pharmacokinetic values were obtained: time (t_{max}) to peak plasma concentration (C_{max}) 2.0–5.8 hours; C_{max} 2.8–3.8 mg/L; area under the plasma concentration-time curve ($AUC_{0-\infty}$) 133.0–228.4 μg h/mL; and half-life ($t_{\frac{1}{2}}$) 36.5–43.4 hours.[31,32] For doses of 7.5–240mg, the overall value for apparent oral clearance (CL/F) was 0.284 L/h; that for the fraction of the vesnarinone dose excreted unchanged in the urine over 14 days was 17.7%, thus indicating the considerable extent to which vesnarinone is metabolized in the body.[31]

After one of the single-dose studies,[31] 3 of the 21 volunteers received vesnarinone 30 mg/day for 15 days. The steady-state was attained after approximately 8–9 days. The mean plasma drug concentrations noted during days 9–14 were 6.29–6.87 mg/L (2 hours post-dose) and 3.61–4.03 mg/L (24 hours post-dose). The mean fraction of the vesnarinone dose excreted unchanged during days 9–15 was 19.2–25.6%. Altogether, this combined single and repeated-dose study indicated log-linear elimination of vesnarinone. Results also suggested that the drug did not induce or inhibit its own metabolism.[31]

An *in-vitro* assessment of blood samples from 12 volunteers revealed the metabolism of vesnarinone to the dehydrogenation product OPC-18692

© Adis Data Information BV 2004. All rights reserved.

via cytochrome P450 (CYP) 2E1 but principally via CYP3A.[32] *In vivo*, CYP3A activity was inhibited by erythromycin pretreatment, a situation confirmed by the erythromycin breath test. Subsequently, among the 12 volunteers, the mean vesnarinone C_{max} increased (+11%, $p < 0.05$), as did $t_{\frac{1}{2}}$ (+27%, $p < 0.01$) and $AUC_{0-\infty}$ (+52%, $p < 0.001$), whereas CL/F was reduced by 31% ($p < 0.001$). These changes indicate that it is clinically prudent to monitor plasma vesnarinone levels in patients receiving concomitant therapy with inhibitors of CYP3A. Whether such monitoring is also necessary in patients receiving inducers of CYP3A remains to be clarified.[32]

4. Clinical Efficacy of Vesnarinone in Patients with End-Stage Heart Failure

Three early, randomized controlled trials of vesnarinone in patients with heart failure revealed encouraging results.[33–35] QOL, for example, significantly improved in all these trials. In a Japanese study of 83 patients with chronic NYHA class II–IV heart failure, 12 weeks' administration of vesnarinone 60 mg/day versus placebo significantly improved general well-being ($p < 0.01$). According to the physicians' global impression of symptoms, 44.4% of vesnarinone-treated patients compared with 13.2% of placebo recipients ($p < 0.01$) were considered 'much better'.[33] Another 12-week study, this time of 76 patients with chronic NYHA class II–IV heart failure, documented a median improvement in QOL [decrease in Sickness Impact Profile (SIP) score] of approximately 50% from baseline ($p < 0.001$) in patients treated with vesnarinone 60 mg/day; the corresponding median change in placebo recipients was approximately 8% (not significant).[34] In the Vesnarinone Study Group Trial (VSGT),[35] almost 500 patients with an ejection fraction < 30% during conventional therapy with an ACE inhibitor (90% of patients) and digoxin (87%) were randomly assigned to receive vesnarinone 60 or 120 mg/day or placebo. After 12 weeks, QOL measured by the overall SIP score had improved significantly more in the vesnarinone than in the placebo group (median score change −4.2 vs −2.5; $p = 0.008$; table I). The QOL difference was also statistically significant regarding the SIP physical ($p = 0.017$) and psychosocial scores ($p = 0.006$).[35]

Favourable effects on morbidity and mortality were also noted in these three early controlled trials.[33–35] In the Japanese study,[33] 8 of 38 placebo recipients (21%) died or were withdrawn from the trial because of worsening heart failure, whereas only one of 45 vesnarinone-treated patients (2%) was withdrawn because of symptom deterioration. The 12-week study of 76 patients with heart failure[34] identified significantly less combined major morbidity and mortality in the vesnarinone than in the placebo group. Two vesnarinone-treated patients (5%) versus nine placebo recipients (24%) died or experienced major clinical deterioration.[34] In the VSGT,[35] initial excess mortality was associated with vesnarinone 120 mg/day, such that patients were withdrawn from this study arm. During the 6-month study period, significantly fewer vesnarinone 60 mg/day than placebo recipients died or required intravenous inotropic therapy (26 vs 50, $p = 0.003$). The corresponding number of deaths was 13 versus 33 ($p = 0.002$; table I), thus representing a 62% decrease in the risk of all-cause mortality in the vesnarinone group. Overall, the discrepancy between increased mortality with the high vesnarinone dosage and reduced mortality with the lower dosage highlighted the narrow therapeutic range of vesnarinone.[35]

Data from the Vesnarinone Trial (VEST) were published relatively recently.[36] Results completely contradicted the favourable mortality findings from the earlier VSGT study.[35] Indeed, VEST evaluated the efficacy of vesnarinone 30 or 60 mg/day or placebo, over a mean follow-up period of 286 days, in a total of 3833 patients with NYHA class III–IV heart failure and ejection fraction ⩽ 30%. Approximately 90% of patients were receiving ACE inhibitor therapy when randomly assigned to vesnarinone 30 or 60 mg/day or placebo. Subsequently, mortality rates were 18.9%, 21.0% and 22.9% in the placebo, vesnarinone 30 mg/day and vesnarinone 60 mg/day

© Adis Data Information BV 2004. All rights reserved.

Table I. Principal results from two large-scale, controlled clinical trials of vesnarinone in patients with heart failure

Study	Design	Duration	Regimens	Number of patients	All-cause mortality (number [%] of deaths)	Combined mortality/ morbidity[a] (number [%] of events)	Median change in QOL score from baseline[b]
Feldman et al. (1993)[35]	r, db, pg, mc	6 months	VES 120 mg/day[c]	–	–	–	–
Vesnarinone Study Group Trial (VSGT)				239	13 (5.4)*	26 (10.9)*	−4.2[d]*
			VES 60 mg/day[c]	238	33 (13.9)	50 (21.0)	−2.5[d]
			PL				
Cohn et al. (1998)[36]	r, db, pg, mc	59–489 (mean 286) days	VES 30 mg/day	1275	268 (21.0)	395 (31.0)	−5[e]
			VES 60 mg/day	1275	292 (22.9)	410 (32.2)	−8[e]*
Vesnarinone Trial (VEST)			PL	1283	242 (18.9)	382 (29.8)	−6[e]

[a]Number (%) of patients who died or had worsening heart failure.

[b]A decrease indicates improvement.

[c]The 120 mg/day regimen was discontinued because of early excess mortality.

[d]Sickness Impact Profile scores measured after 12 weeks of treatment.

[e]Scores on the Minnesota Living with Heart Failure questionnaire at 16 weeks after randomization.

db, double-blind; mc, multicentre; pg, parallel group; PL, placebo; QOL, quality of life; r, randomized; *$p \leq 0.008$ vs PL.

© Adis Data Information BV 2004. All rights reserved.

groups, respectively. A significantly shorter time to death from any cause was noted in the higher-dosage vesnarinone versus placebo group ($p = 0.02$); however, the trend towards a similar adverse effect was not statistically significant in the lower-dosage vesnarinone versus placebo group ($p = 0.21$). The rate of the combined endpoint of all-cause mortality, or major morbidity resulting from heart failure, was greater in vesnarinone-treated patients than placebo recipients (31.0–32.2% vs 29.8%; table I). Overall, greater mortality in the vesnarinone groups than the placebo group was attributed to sudden death, the rates of which were 10.7–12.3% versus 9.1%.[36]

Consideration of VEST data,[36] together with results for vesnarinone 120 mg/day from the VSGT trial,[35] outline an almost-linear, detrimental dose–response effect for vesnarinone on mortality. However, in VEST, and in agreement with previous studies, vesnarinone 60 mg/day versus placebo significantly improved QOL after 8 ($p < 0.001$) and 16 ($p = 0.003$, table I), but not after 26 weeks of treatment. This underscores an important principle: namely, patients with end-stage heart failure are often willing to accept an increased risk of mortality as a 'trade-off' for short-term QOL enhancement.[36] Another important issue is contention about the potential deleterious effects associated with the discontinuation of inotropic therapy. Nevertheless, among 1140 patients enrolled in a withdrawal sub-study of VEST, 12.7% entered another clinical trial, 9.3% died, 1.5% had a heart transplant, and 1.5% were lost to follow-up.[37] The study arm of VEST from which patients were withdrawn had no significant influence on outcome; specifically, the discontinuation of vesnarinone at completion of the VEST study was not associated with an adverse outcome.[37] Other differences were notable in the VEST and VSGT study populations. In VEST, patients did not have to be able to exercise, compared with patients in the VSGT study who all underwent exercise testing with respiratory gas exchange during the study. Furthermore, by contrast with VSGT, VEST patients did not undergo monitoring of digoxin levels and had higher mean mealtime levels.

5. Role of Vesnarinone in the Management of Refractory End-Stage Heart Failure

As previously highlighted, the central pharmacological features of disease management in patients with heart failure are ACE inhibitors, β-blockers and diuretics, as well as anti-aldosterone agents in patients with more severe disease (figure 1).[1,2,5,7–10] Much clinical evidence has confirmed the mortality-reducing benefits of β-blockers, ACE inhibitors and spironolactone in patients with heart failure,[2,5,10] whereas evidence for such benefit associated with diuretics and digoxin is lacking.[7,9] Nevertheless, diuretics and digoxin have well-defined haemodynamic and symptomatic benefits in patients with heart failure,[1] although the role of digoxin in the treatment of women with heart failure is more open to question.[38] Despite optimal treatment, some heart failure patients (perhaps up to approximately 5%) do not obtain symptomatic relief at rest. Inotropic agents (e.g. vesnarinone) that markedly improve symptoms and QOL, but have no survival benefit, may be appealing to heart failure patients with persistent symptoms.[9] That is, some patients are willing to accept an increased risk of death in the hope of obtaining symptomatic improvement during their remaining lifespan.[2,9,36] In fact, in one study of ambulatory patients with NYHA class III–IV heart failure, approximately half of the patients expressed a willingness to trade-off ⩾ 50% of their remaining time alive to feel better.[9]

The pharmacodynamic assessment of patients with severe refractory heart failure showed vesnarinone to improve biventricular performance most in patients with the worst degree of initial impairment.[24] The most favourable risk–benefit ratio of vesnarinone was thus evident in patients with the most severe symptoms of heart failure. These patients are generally most willing to exchange reduced survival for improved QOL.[9] Certainly, when considering the long-term use of vesnarinone in patients with refractory end-stage heart failure, clinicians must assess the individual risk–benefit for each patient.[35] Although vesnar-

© Adis Data Information BV 2004. All rights reserved.

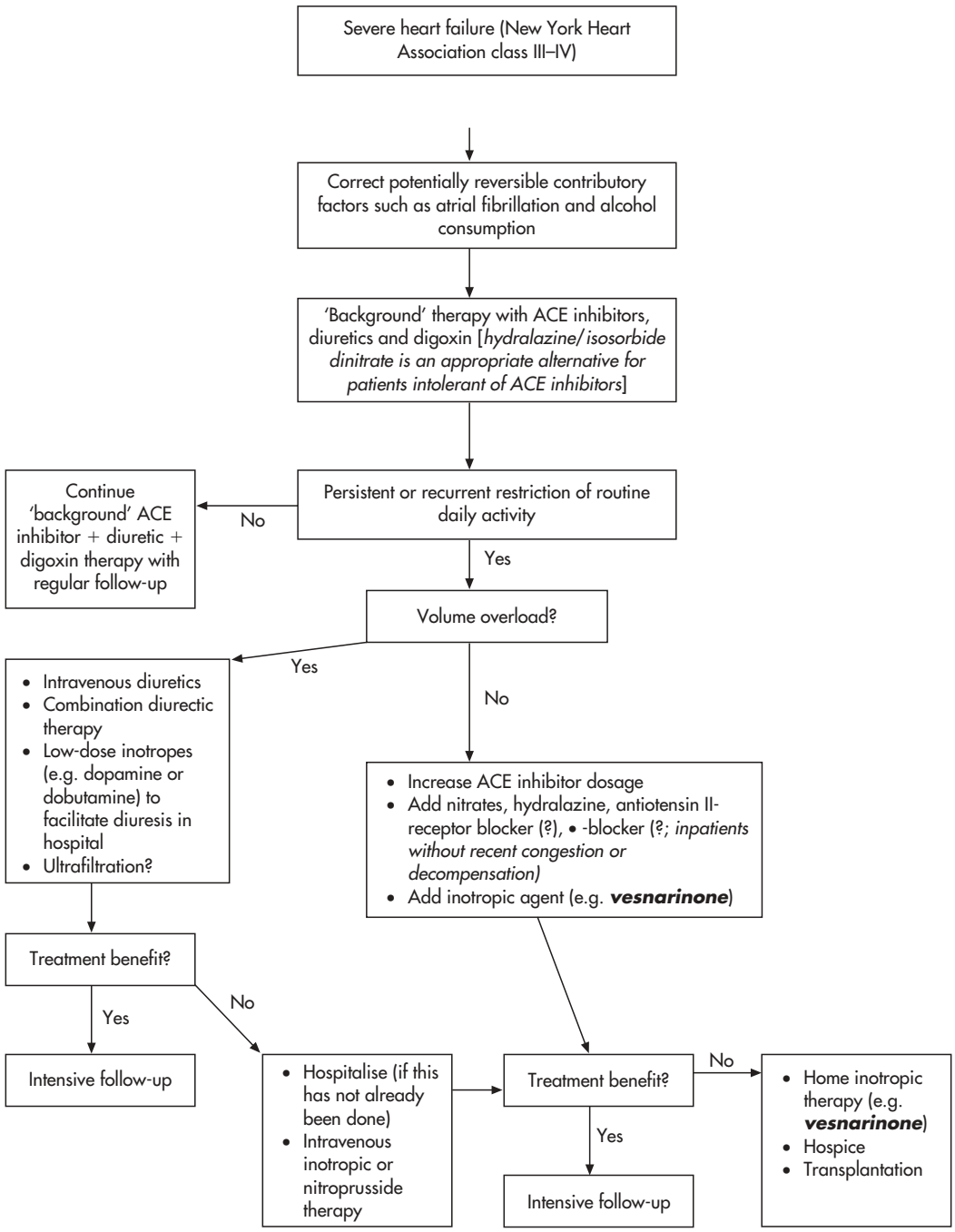

Fig. 1. Suggested basic algorithm, highlighting the potential clinical role of vesnarinone, for the management of refractory end-stage heart failure. **ACE** = Angiotensin-converting enzyme.

© Adis Data Information BV 2004. All rights reserved.

inone was clearly associated with increased mortality in the VEST trial, much of this mortality resulted from sudden death.[36] The future use of implantable defibrillators may reduce such mortality.[9] Overall, therefore, vesnarinone may attain an established role in the management of the relatively small percentage of heart failure patients with end-stage disease refractory to 'primary' pharmacotherapy. This role might also involve an important function for vesnarinone as a pharmacological 'bridge' to cardiac transplantation.[14] Nonetheless, further detailed investigation is certainly needed to clarify the clinical role of vesnarinone in refractory end-stage heart failure.

Recent preliminary findings have indicated that inotropic agents such as vesnarinone may also develop an important place, together with β-blockers, in the long-term treatment of advanced heart failure. β-Blockers are established treatments for mild-to-moderate heart failure, and combination therapy with a β-blocker plus low-dose phosphodiesterase inhibitor now seems theoretically appealing in advanced heart failure. The individual agents in such a two-drug combination schedule may have additive efficacy and may cancel out each other's adverse effects.[14,15] This possibility is now being evaluated using low doses of the phosphodiesterase inhibitor enoximone in inotrope-dependent patients as well as in patients with class III–IV symptoms who require both vesnarinone and a β-blocker.

6. Conclusions

Haemodynamic studies in patients with chronic heart failure have indicated that vesnarinone has modest, dose-dependent, positive inotropic activity with minimal negative chronotropic activity. Experimental studies identified several possible mechanisms for these vesnarinone effects, but precisely which mechanisms account for the pharmacodynamic and clinical properties of vesnarinone in patients with heart failure awaits clearer definition.[20]

In the clinical setting of advanced-stage heart failure, combined data from the VEST trial,[36] and for the vesnarinone 120 mg/day regimen used in the VSGT trial,[35] indicated a dose-dependent deleterious effect for vesnarinone on mortality across the dose range 30–120 mg/day. Nevertheless, 8–16 weeks' vesnarinone 60 mg/day was associated with statistically significant improvements in QOL in the two studies. Some patients with refractory end-stage heart failure may be willing to trade-off a slightly increased risk of death for short-term improvements in QOL in their remaining time alive. Vesnarinone may therefore develop established clinical utility in such patients. However, much further study is needed to document definitively the overall place of vesnarinone in heart failure management. Of particular interest in this regard is the possibility that vesnarinone plus β-blocker therapy may prove clinically beneficial in patients with advanced-stage heart failure. Furthermore, the use of an inotropic agent in patients with an implantable cardioverter-defibrillator (with or without a resynchronization device) might also be of interest.

References

1. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. Am Heart J 1998; 135: S293-S309
2. Armstrong PW, Moe GW. Medical advances in the treatment of congestive heart failure. Circulation 1994; 88: 2941-52
3. Feldman AM. Pharmacologic properties and clinical evaluation of the new inotropic agent OPC-8212 (vesnarinone). Cardiovasc Drug Rev 1993; 11: 1-11
4. Reddy S, Benatar D, Gheorghiade M. Update on digoxin and other oral positive inotropic agents for chronic heart failure. Curr Opin Cardiol 1997; 12: 233-41
5. Dracup K. Heart failure secondary to left ventricular systolic dysfunction. Therapeutic advances and treatment recommendations. Nurse Pract 1996; 21: 56-68
6. Nielsen-Kudsk JE, Aldershvile J. Will calcium sensitizers play a role in the treatment of heart failure? J Cardiovasc Pharmacol 1996; 26 (Suppl. 1): S77-S84
7. Carson P. Pharmacologic treatment of congestive heart failure. Clin Cardiol 1996; 271-7
8. Bonarjee VVS, Dickstein K. Novel drugs and current therapeutic approaches in the treatment of heart failure. Drugs 1996; 51: 47-58
9. Stevenson LW. Inotropic therapy for heart failure. N Engl J Med 1998; 339: 1848-50
10. Forker AD. A cardiologist's perspective on evolving concepts in the management of congestive heart failure. J Clin Pharmacol 1996; 36: 973-84
11. Shakar SF, Bristow MR. Low-level inotropic stimulation

© Adis Data Information BV 2004. All rights reserved.

with type III phosphodiesterase inhibitors in patients with advanced symptomatic chronic heart failure receiving β-blocking agents. Curr Cardiol Rep 2001; 3: 224-31
12. Bristow MR. β-Adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101: 558-69
13. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS study. JAMA 2003; 289: 712-18
14. Chatterjee K, Wolfe CL, DeMarco T. Nonglycoside inotropes in congestive heart failure. Are they beneficial or harmful? Cardiol Clin 1994; 12: 63-72
15. Lowes BD, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. Clin Cardiol 2000; 23 (Suppl. III): S11-S6
16. Baughman K. New medical therapies for advanced left ventricular dysfunction. Cardiol Clin 1995; 13: 27-34
17. Uchida Y, Kawada M, Sawanobori K, et al. Cardiovascular effects of (2RS,3SR)-2-aminomethyl-2,3,7,8-tetrahydro-2,3,5,8,8-pentamethyl-6H-furo-[2,3-e]indol-7-one hydrochloride (UK-1745), a novel cardiotonic agent with vasodilatory and antiarrhythmic properties. Arzneim Forsch Drug Res 1998; 48: 219-31
18. Lathrop DA, Nánási PP, Schwartz A, Varró A. Ionic basis for OPC-8212-induced increase in action potential duration in isolated rabbit, guinea pig and human ventricular myocytes. Eur J Pharmacol 1993; 240: 127-37
19. Toyama J, Kamiya K, Cheng J, et al. Vesnarinone prolongs action potential duration without reverse frequency dependence in rabbit ventricular muscle by blocking the delayed rectifier K^+ current. Circulation 1997; 96: 3696-703
20. Ross JS, Goldfine SM, Herrold EM, Borer JS. Differential response to vesnarinone by cardiac fibroblasts isolated from normal and aortic regurgitant hearts. Am J Ther 1998; 5: 369-75
21. Gilbert EM, Renlund DG, Olsen SL, et al. Hemodynamic and neuroendocrine effects of chronic vesnarinone administration in heart failure: a placebo-controlled trial. J Am Coll Cardiol 1994 Feb; Special Issue: 173A
22. Asanoi H, Sasayama S, Kameyama T, et al. Sustained inotropic effects of a new cardiotonic agent, OPC-8212, in patients with chronic heart failure. Clin Cardiol 1989; 12: 133-8
23. Kass DA, Van Anden E, Becker LC, et al. Dose dependence of chronic positive inotropic effect of vesnarinone in patients with congestive heart failure due to idiopathic or ischemic cardiomyopathy. Am J Cardiol 1996; 78: 652-6
24. Scherrer-Crosbie M, Cocca-Spofford D, DiSalvo TG, et al. Effect of vesnarinone on cardiac function in patients with severe congestive heart failure. Am Heart J 1998; 136: 769-77
25. Matsumori A, Sasayama S. Immunomodulating agents for the management of heart failure with myocarditis and cardiomyopathy – lessons from animal experiments. Eur Heart J 1995; 16 (Suppl. O): 140-3
26. Matsui S, Matsumori A, Matoba Y, et al. Treatment of virus-induced myocardial injury with a novel immunomodulating agent, vesnarinone. Suppression of natural killer cell activity and tumor necrosis factor-α production. J Clin Invest 1994; 94: 1212-7
27. Kambayashi T, Mazurek N, Jacob CO, et al. Vesnarinone is a selective inhibitor of macrophage TNFα release. Int J Immunopharmacol 1996; 18: 371-8
28. Matsui S, Matsumori A, Sasayama S. Vesnarinone prolongs survival and reduces lethality in a murine model of lethal endotoxemia. Life Sci 1994; 55: 1735-41
29. Matsumori A, Furukawa Y, Shioi T, Matsui S. Vesnarinone inhibits production of interleukin 1, tumor necrosis factor-α and interferon-γ by peripheral blood from patients with heart failure. Circulation 1994; 90: 2940
30. Deswal A, Petersen NJ, Feldman AM, et al. Effects of vesnarinone on peripheral circulating levels of cytokines and cytokine receptors in patients with heart failure. Chest 2001; 120: 453-9
31. Ohnishi A, Ishizaki T. Pharmacokinetic profile of OPC-8212 in humans: a new, nonglycosidic, inotropic agent. J Clin Pharmacol 1988; 28: 719-26
32. Wandel C, Lang CC, Cowart DC, et al. Pharmacokinetics and drug disposition. Effect of CYP3A inhibition on vesnarinone metabolism in humans. Clin Pharmacol Ther 1998; 63: 506-11
33. Fujiwara H, Fukunami M, Hirosawa K, et al. A placebo-controlled, randomized, double-blind study of OPC-8212 in patients with mild chronic heart failure. Cardiovasc Drug Ther 1990; 4: 419-26
34. Feldman AM, Baughman KL, Lee WK, et al. Usefulness of OPC-8212, a quinolinone derivative, for chronic congestive heart failure in patients with ischemic heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1991; 68: 1203-10
35. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. N Engl J Med 1993; 329: 149-55
36. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med 1998; 339: 1810-6
37. Soran O, Young J, White BD, Feldman AM. Withdrawal of the inotropic agent vesnarinone is not associated with an adverse outcome: substudy results from the VesT trial. J Am Coll Cardiol 1999; 33 (Suppl. A): 200A
38. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002; 347: 1403-11

Correspondence and offprints: *Arthur M. Feldman*, Chair, Department of Medicine, Thomas Jefferson University Hospital, 925 Chestnut Street, Messainine, Philadelphia, PA 19107, USA.
Fax: +1 215 955 2318;
E-mail: arthur.feldman@jefferson.edu

© Adis Data Information BV 2004. All rights reserved.