Editorial

How Many Medicines Do Patients With Heart Failure Need?

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Over the past 2 decades, a number of controlled clinical trials have been performed that have taught us that polypharmacy for heart failure is necessary to achieve the best reduction in morbidity and mortality. Four drugs are given to patients with moderately severe heart failure: digoxin, a loop diuretic, an ACE inhibitor, and a β-blocker. Although no mortality trials have been done with diuretics, the clinical experience is that they are both necessary and effective agents for reducing volume overload and decreasing symptoms of dyspnea. Although the Digitalis Investigation Group did not show any reduction in mortality with digoxin, there was a reduction in the hospitalization rate.1 Furthermore, other trials have shown clinical benefit with this drug. Both ACE inhibitors and β-blockers have a plethora of evidence showing that they reduce mortality and morbidity in patients with heart failure.2–5 In class IV patients, the aldosterone antagonist spironolactone also reduced mortality.6 Whether spironolactone is also beneficial in less severe heart failure is not known, but it is increasingly being used in that setting. Some data indicate that β-blockers may be helpful in patients with class IV heart failure (Carvedilol Prospective Randomized Cumulative Survival [COPERNICUS] Trial; presented at 22nd Congress of European Society of Cardiology, August 2000). Thus, there are now 5 agents that can be considered part of standard therapy for heart failure. Despite this effective pharmacotherapy, however, patients continue to slide downhill over time and, although physicians reduce mortality with these drugs, the curve is merely shifting to the right.

See Circulation. 2001;103:1044–1047

This sets the stage for additional therapy that might add to the established drugs mentioned above. It should be apparent, however, that a trial of any new therapy must be versus placebo on top of standard therapy. This makes it increasingly difficult to find new agents that will have the incremental benefit necessary to add them to the above regimens. Candidate agents include angiotensin-receptor blockers, neutral endopeptidase inhibitors, endothelin antagonists, and cytokine antagonists. It is also important to define what additional benefit would be sufficient to establish that new drug as part of the armamentarium for heart failure. For example, in the recent Valsartan-Heart Failure Trial (Val-HeFT), the addition of an angiotensin-receptor blocker on top of an ACE inhibitor did not further reduce mortality, although it did reduce the hospitalization rate (Val-HeFT; presented at 73rd Scientific Sessions of the American Heart Association, November 2000). Is that enough to consider routinely adding an angiotensin-receptor blocker to an ACE inhibitor? The answer is not clear because the patients receiving both an ACE inhibitor and a β-blocker did not benefit from the addition of an angiotensin-receptor blocker. Does this represent too much neurohormonal antagonism?

However, it is theoretically appealing to consider a whole new class of drugs that might work by an entirely different and novel mechanism. The agents that antagonize cytokines are one such class.7 Cytokines are hormone-like proteins that foster communication between immune cells. Cytokines are produced in lymphocytes, macrophages, fibroblasts, and endothelial cells. Once a factor has been well characterized, it receives an interleukin designation (such as IL-2). Tumor necrosis factors (TNF) α and β, platelet-derived growth factor, and other molecules have not yet been designated in the interleukin series.

Like the neurohormones, elevated levels of the proinflammatory cytokines have prognostic significance. Measurements of TNF-α, soluble TNF receptors 1 and 2 (naturally occurring modulators of TNF-α activity), interleukin-6 (IL-6), and soluble CD14 were made at baseline and after 24 months in 152 patients with heart failure. By multivariate analysis, TNF receptor 1 was the strongest predictor of prognosis.8

In heart failure, much of the TNF-α may actually come from the heart itself.9 In transgenic mice with overexpressed TNF-α, fibrosis, dilatation, and dysfunction occur.10 TNF-α may have a number of adverse effects in heart failure, including cardiac depression, vasodilation, cachexia, and elevations of the renin-angiotensin system. It impairs synthesis and increases catabolism of protein in skeletal muscle, and it may induce cardiac myocyte apoptosis. There is a relationship between elevations of TNF-α and the severity of the heart failure. The important question is whether TNF-α blockade can produce benefit in patients with heart failure.

In a recent issue of Circulation, Bozkurt and colleagues11 reported on the effects of an antagonist of TNF-α in patients with heart failure. Etanercept is a recombinant human TNF receptor that binds to TNF in vitro and in vivo and can thus reverse some of its adverse effects. They studied 47 patients who were in New York Heart Association functional class III to IV who were already being treated with standard therapy; about half of the patients were on β-blockers. The study was randomized, double-blind, and placebo-controlled, and it...
used doses of either 5 mg/m² or 12 mg/m² twice weekly subcutaneously for 3 months. There was a dose-related decline in end-systolic and end-diastolic volumes in the etanercept-treated patients compared with placebo. Similarly, there was a slight increase in ejection fraction compared with a decline in the placebo group. There was a trend toward clinical improvement using a clinical composite score. Etanercept did not affect heart rate or blood pressure. Treatment led to an increase in IL-10 and an improved ratio of anti- to pro-inflammatory cytokines.

This encouraging data is certainly a basis for larger, ongoing trials that must show some significant reduction in morbidity and/or mortality for clinicians to consider this form of therapy as the sixth class of drugs to give in heart failure. Three larger studies are ongoing to test whether etanercept will have longer lasting benefit and to test it in larger populations. (The studies are RENAISSANCE, RECOVER, and RENEWAL).

Several issues need to be remembered with the present study. There are no data on what happened to the patients after completion of the study and withdrawal of the drug. Such data would have been an important confirmation of longer, continued benefit. Although the benefit seemed to be present with or without the use of β-blockers, the database is small. In an animal model, β-blockade had differential effects on TNF and IL-1 compared with IL-6. This concept needs to be explored further in larger clinical trials. The timing and number of blood samples for sampling cytokines is important. Thus, data obtained over a relatively short time period may be difficult to interpret because of natural fluctuations.

Whenever one has encouraging initial results, it is wise to remember that not every drug that helps initially is necessarily a good long-term treatment. Examples include the phosphodiesterase inhibitors, which markedly improved exercise tolerance and left ventricular function in the short-term but increased long-term mortality. In addition, β-blockers may worsen function and symptoms initially, but in the long run, they can produce substantial benefit, including a reduction in mortality. Remember also that vesnarinone, which tends to reduce TNF, seemed to reduce mortality in one study but in a larger study led to an increase in mortality. Thus, it is very difficult to predict up front what the results of the larger trials will be. One thing is sure: we must have those larger trials before we can consider the routine use of such therapy, particularly when it must be given by subcutaneous injection.

The present report, however, may well be the beginning of a whole new way to reduce the rate at which heart failure progresses. Of course, it goes without saying that the best way to treat heart failure is to prevent it, but that is another story.

References


Key Words: Editorials ■ heart failure ■ remodeling
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Circulation. 2001;103:1611-1612
doi: 10.1161/01.CIR.103.12.1611

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