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Scientific Update™

AT_1 receptor blockade – New possibilities in heart failure

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Heart failure is a clinical condition with significant mortality and morbidity.[1] Patients who suffer from heart failure often require repeated hospital admissions.[2] In fact, hospitalization is a key manifestation of heart failure morbidity, accounting for 70% of its total health care cost. Heart failure also accounts for more than 5% of all emergency medical admissions. Recent data suggest that the annual rate of hospitalization for heart failure is increasing in many countries, including the United States, Sweden, the Netherlands, and Spain,[1] and it is possible a similar increasing trend exists in other industrialized countries. The prognosis of patients with heart failure continues to be poor. In the recently published Cardiac Insufficiency Bisoprolol Study II (CIBIS-II),[3] patients on optimal conventional therapy for heart failure, randomized to the placebo arm of the study, had an annual all-cause mortality rate of 12%, all-cause hospital admission rate of 39%, and hospitalization rate for worsening heart failure of 18%. Not surprisingly, clinicians continue to look for pharmacologic agents that will improve these high event rates in patients with heart failure.

Angiotensin-converting enzyme (ACE) inhibitors are of proven clinical benefit in patients with heart failure who also have impaired systolic left ventricular function.[4,5] Recently, spironolactone, an agent that blocks aldosterone, another component of the renin-angiotensin-aldosterone system (RAAS), was shown to reduce mortality and morbidity when added to ACE inhibitor therapy in heart failure patients with advanced symptoms. With the recent introduction of the selective angiotensin II type 1 (AT_1) receptor blockers (ARBs), there are key questions regarding their role in heart failure. First, are the ARBs better than placebo? Second, are they more effective than ACE inhibitors? Third, will combination therapy with an ARB and an ACE inhibitor be superior to monotherapy with either agent? The following report will describe some of the studies that are offering some clues, as well as ongoing large-scale trials that will eventually provide definitive answers to these questions.

AT_1 receptor blockade, a novel therapeutic concept

AT_1 receptor blockers, by selectively binding to AT_1 receptors, prevent the deleterious effects of angiotensin II, no matter whether angiotensin II is generated from ACE or the "alternative pathways" (Table 1). Furthermore, selective AT_1 receptor blockade may result in increased stimulation of the angiotensin II type 2 (AT_2) receptor subtypes, possibly antagonizing the vasoconstrictive and proliferative effects from AT_1 receptor stimulation by angiotensin II.[6] On the other hand, ARBs do not enhance kinins to the same degree as the ACE inhibitors, an effect believed to mediate ACE inhibitor-induced cough.[7] Indeed, the ARBs appear to be remarkably well tolerated. Studies of these agents to date have demonstrated close to placebo-like tolerability, both in patients with hypertension and in those with heart failure.[8,9]

In addition to the unique pharmacologic actions already mentioned, the newer ARBs have another feature: a long duration of action. One ARB, candesartan cilexitil, appears to exhibit a clear dose-dependent blood pressure lowering effect across a wide dose range in patients with hypertension.[10] As demonstrated in the recently-reported Candesartan in Hypertension Ambulatory Monitoring of Blood Pressure (CHAMP) study, this drug administered once daily, compares

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favourably to losartan on the basis of its improved blood pressure control during continuous monitoring more than 36 hours after dosing.[11] This finding is further supported by candesartan's trough:peak ratio that approaches 1. Also, this long-lasting effect may be related to the insurmountable binding characteristics of candesartan cilexetil.[12] In a recent study of 926 patients with heart failure, candesartan cilexetil treatment appeared to produce a dose-dependent improvement in exercise tolerance as measured by treadmill walking time when compared to placebo. This was accompanied by an improvement in symptoms of heart failure.[13] Whether this longer-lasting hemodynamic effect will translate to better cardioprotection in patients with heart failure remains to be confirmed by results pending from large-scale studies that will be discussed below.

AT_1 receptor blockers in heart failure

Experimental studies have now identified multiple mechanisms by which an overactivation of the RAAS could be detrimental in heart failure. At first it was believed that ACE inhibitors exerted their beneficial effects primarily by reducing the conversion of angiotensin I to angiotensin II. However, it is now known that ACE inhibitors block the formation of angiotensin II incompletely, due in part to the presence of "alternative pathways" of generation of angiotensin II. For example, studies that evaluated the effect of the ACE inhibitor enalapril in patients with essential hypertension revealed "escape" of plasma angiotensin II over time.[14] Furthermore, in the SOLVD (Studies Of Left Ventricular Dysfunction) study, patients who suffered clinical deterioration and progression of left ventricular dysfunction had plasma angiotensin II levels three times higher than stable patients.[15] As shown in Figure 1, ACE is also kinase II, the enzyme that breaks down bradykinin to inactive kinin fragments. Increased bradykinin as a result of ACE inhibition produces increased vasodilator prostaglandins and nitric oxide, with accompanying vasodilatory, anti-proliferative and anti-thrombotic effects. Indeed, animal studies with concomitant administration of specific antagonists of bradykinin receptors have strongly suggested that enhancement of the bradykinin-nitric oxide pathway is a particularly important mechanism for producing beneficial effects from ACE inhibitors in heart failure.[16-18] While these data need to be confirmed in clinical studies, they provide a rationale for the studies of combined therapy with ACE inhibitors and ARBs.

Early ARB clinical trials

Clinical experience with the use of ARBs in heart failure is still limited. Studies published to date have involved small patient sample size that only examined surrogate endpoints of efficacy and tolerability. None had sufficient power to assess mortality.

Table 1: Physiologic and pathologic effects of angiotensin II mediated by its receptor subtypes

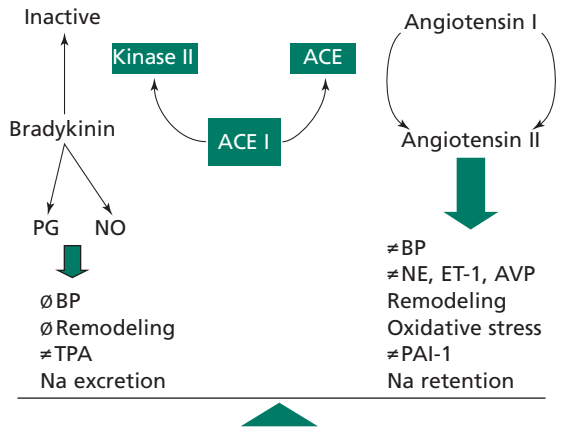
AT_1 receptor	AT_2 receptor
≠Vasoconstriction	Vasodilation
≠sympathetic tone	Anti-trophic and anti-proliferative effects
≠endothelin-1	Apoptosis
≠cellular hypertrophy and proliferation	≠nitric oxide
≠oxidative stress	
≠plasminogen activator inhibitor-1	
≠sodium reabsorption	
≠fibrosis	

In 1995, the first of the clinical trials of ARBs in heart failure, a multinational Scandinavian trial, was reported.[19] In this trial, 166 patients with New York Heart Association (NYHA) class III and IV symptoms were randomized to receive losartan 25 mg daily, losartan 50 mg daily, and enalapril 20 mg daily for eight weeks. The primary endpoints were exercise tolerance as measured by a six-minute walk test, clinical and neurohormonal status. There were no significant differences between treatment groups in exercise tolerance, dyspnea-fatigue index, neurohormonal activation, left ventricular ejection fraction, or worsening of heart failure.

A study with similar design, same sample size and primary endpoints, was conducted in North America by the Losartan Pilot Exercise Study Investigators.[20] Like the Scandinavian study, there were no significant differences between the treatment arms in any of the surrogate endpoints. Interestingly, there was a non-significant difference in deaths (5 in losartan 50 mg, 1 in losartan 25 mg, and none in the enalapril group).

The Evaluation of Losartan In The Elderly (ELITE) study was another pilot study designed to evaluate the safety and efficacy of losartan in elderly patients with heart failure compared with that of the ACE inhibitor captopril.[8] Seven hundred and twenty two patients with NYHA II to IV (mostly class II) symptoms were randomized to losartan 50 mg daily or captopril 150 mg daily. The primary endpoint was renal function (a persistent increase in serum creatinine ≥ 26.5 µmol/L). The secondary endpoint was composite of death and/or hospitalization for heart failure. After 48 weeks, there was no difference between groups in the frequency of sustained rise in serum creatinine (10.5% in both groups). However, tolerability was significantly better in the losartan-treated patients, with fewer patients discontinuing the medication early (12.2%) compared to the captopril-treated patients (20.8%). Although there was no significant difference in the primary or compos-

Figure 1: Mechanisms of action of ACE inhibitors



BP = blood pressure
PG = vasodilator prostaglandins
NO = nitric oxide
NE, ET-1 and AVP = norepinephrine, endothelin-1 and arginine vasopressin
TPA, PAI-1 = tissue plasminogen activator and plasminogen activator inhibitor-1.

ite secondary endpoint, one unexpected finding was a significant difference in total mortality (4.8% in the losartan group, 8.7% in the captopril group; RR 0.54, CI 0.31, 0.95, p=0.035). This difference was primarily due to a reduction in sudden cardiac death. To confirm these findings, the 2640 patient ELITE-II study, with total mortality as primary endpoint, is currently underway and is near its completion.

Trials of combination therapy

The first study to address the issue of combination therapy with both an ACE inhibitor and an ARB was the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study. In this pilot study, 768 patients with NYHA II to IV symptoms and left ventricular ejection fraction <40% were randomized to candesartan cilexetil alone (4, 8, or 16 mg), combination therapy (candesartan 4 or 8 mg with enalapril 20 mg daily), or enalapril 20 mg daily. The primary endpoints were six-minute walk distance, safety, tolerability, neurohormonal status, left ventricular ejection fraction, and quality of life. (Key results of this trial have been reported in a previous issue of *Cardiology Scientific Update*). There were no significant differences between candesartan cilexetil and enalapril on most of the endpoints. However, the combination therapy was more effective in suppressing plasma aldosterone and natriuretic peptide levels, which improved left ventricular ejection fraction, preventing the increase of ventricular volumes and the reduction in arterial pressure.[21] All three regimens were well tolerated. There were no differences between the three groups in death or hospitalization rates although the study was not designed to monitor clinical events. The RESOLVD results support further study of combined ACE inhibitor and ARB therapy in heart failure.

When patients cannot tolerate ACE inhibition

In clinical practice, clinicians often encounter patients with heart failure who are intolerant to ACE inhibitors. These patients are therefore denied the benefits of ACE inhibition. The Study of Patients Intolerant of Converting Enzyme inhibitors (SPICE) was designed to assess the effects of the ARB candesartan cilexetil in such patients.[22] In the SPICE registry, 9580 patients with left ventricular ejection fraction of < 35% were surveyed in 107 centers from eight countries between 1996-1997. Nine percent of patients were withdrawn from ACE inhibitor therapy due to intolerance to the drug because of cough, renal insufficiency, or hypotension. Two hundred and seventy of these ACE-intolerant patients were randomized in a 2:1 ratio to candesartan (4, 8, or 16 mg) or placebo. The median age of these 270 patients was 67 years, 71% had heart failure due to coronary artery disease, and NYHA functional class was II for 54% and III for 41%. The intolerance was due to cough, hypotension and renal dysfunction in 67%, 15%, and 11% of the patients respectively. The primary endpoint of the pilot study was tolerability, while the secondary endpoints included safety, clinical events, functional status, and quality of life. The overall result was that candesartan cilexetil was well tolerated; the assigned treatment was continued to 12 weeks in 82.7% of patients given candesartan, compared to 86.6% of patients given placebo (difference not significant). The results of SPICE indicate that patients who cannot tolerate ACE inhibitors can benefit from candesartan cilexetil, and supports further studies of ARBs in patients with heart failure who are intolerant of ACE inhibitors.

Many ambulatory as well as hospitalized patients with heart failure have preserved left ventricular ejection fraction.[23-25] The current treatment of patients with heart failure who have normal systolic function remains empirical.[26] Although some studies suggest that the prognosis for these patients may be more favorable than for those patients with impaired systolic function,[23,25] the mortality rate is still significantly higher than for age-matched control subjects.[25] The prevalence of the condition and the unfavorable prognosis underscore the need for controlled trials to define the best treatment for patients with heart failure and preserved systolic function.

Candesartan cilexetil in heart failure management – the CHARM program

CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) is a large outcome

study designed to define the clinical benefits of the ARB candesartan cilexetil in a broad spectrum of patients with symptomatic left ventricular dysfunction. CHARM is a unique study because it will evaluate patients with heart failure and preserved systolic function as well as reduced left ventricular ejection fraction. This trial will recruit 6500 patients from 26 countries and will consist of 3 integrated clinical trials involving different patient groups as follows:

- Patients with reduced left ventricular ejection fraction (LVEF ≤ 40%) who are intolerant to ACE inhibitors
- Patients with LVEF ≤ 40% and treated with an ACE inhibitor (combination therapy)
- Patients with preserved left ventricular function (LVEF > 40%) who are not treated with an ACE inhibitor

In each of the study arms, patients will be randomized to treatment with either candesartan cilexetil or placebo. The primary objective of each of the 3 trials is to examine the effects on the combined endpoint of cardiovascular mortality or heart failure hospitalization. The program is designed such that the 3 studies can be combined to evaluate the effect of candesartan cilexetil on all-cause mortality. CHARM will therefore have the ability to address the question of whether candesartan can meet the need for a better therapy in different subgroups of patients of heart failure and overcome some of the limitations of the presently available therapies. CHARM is the largest investigation to be conducted in patients with heart failure. The first patient was recruited in the first quarter of this year. At the time of writing of this report, 3744 patients have been screened. The average follow-up will be 2.7 years. It is anticipated that randomization will end in the third quarter of 2000, the study will end in the third quarter of 2002 with results available at the second quarter of 2003.

Summary

In conclusion, the use of ARBs in heart failure is an active area of research. Studies to date have been pilot studies using surrogate endpoints. Results so far demonstrate that these agents provide equivalent hemodynamic effects and control of symptoms compared to ACE inhibitors but they appear to be better tolerated than ACE inhibitors. It is, however, unclear whether these agents will provide equal survival benefit as the ACE inhibitors although data obtained from the ELITE study are encouraging. The soon-to-be completed ELITE-II study will hopefully provide a definitive answer to this question. Results from the SPICE study indicate that selected patients who are intolerant to ACE inhibitors can tolerate an ARB such as candesartan cilexetil. The combined use of ACE inhibitors and ARBs is theoretically appealing with encouraging data derived from surrogate endpoints in the RESOLVD study. The impact of combination therapy on patient mortality will await the results of the ongoing 5000 patient Val-HeFT (Valsartan-Veterans Affairs Vasodilator-Heart Failure Trials) study as well as the CHARM study.

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