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Heart Failure: Is There a Role for Angiotensin II Receptor Blockers?

Summary

- **Angiotensin II receptor blockers (ARBs) directly inhibit the angiotensin II type 1 receptors, which suppresses the renin-angiotensin-aldosterone system (RAAS).**
- **Six ARBs are approved in Canada for the treatment of hypertension, none are yet approved for the treatment of heart failure (HF).**
- **Evidence comparing ARBs to angiotensin converting enzyme inhibitors (ACEIs) in HF is still limited. A recent meta-analysis of 17 clinical trials could not confirm that ARBs are superior to ACEIs in reducing either mortality or hospitalization in HF patients. ARBs may be used as an alternative in HF patients intolerant of ACEIs.**
- **A meta-analysis indicates that, compared to using an ACEI alone, adding an ARB to an ACEI carries the potential for additional benefits in terms of reduced hospitalization, but not mortality. However, the FDA determined there is currently insufficient evidence of such additional benefit when valsartan is combined to an ACEI in patients with HF.**

The Technology

Currently, ACEIs are considered the mainstay in the treatment of HF as they have been shown to decrease morbidity and mortality.[1] This effect may be derived from their ability to suppress neurohormonal activation in the RAAS.[1]

By directly inhibiting the angiotensin II type 1 receptor, ARBs suppress the RAAS differently than ACEIs, which may carry the potential for additional benefits in the treatment of HF.[1] Also, unlike ACEIs, ARBs do not suppress the breakdown of bradykinin, which may cause intractable cough in 10% of patients with HF.[1]

Regulatory Status

Six ARBs are currently approved for the treatment of hypertension in Canada: candesartan cilexetil (Atacand®) by AstraZeneca, eprosartan mesylate (Teveten®) by Solvay Pharma, irbesartan (Avapro®) by Bristol-Myers Squibb/Sanofi-Synthelabo, losartan (Cozaar®) by Merck Frosst, telmisartan (Micardis®) by Boehringer Ingelheim, and valsartan (Diovan®) by Novartis. None are approved yet for the treatment of HF in Canada. Valsartan was recently approved for this indication in the US for the treatment of HF in patients intolerant of ACEIs.[2]

Patient Group

HF affects more than 400,000 Canadians, with over 50,000 new cases occurring each year.[3] The one-year mortality rate ranges from 25 to 40%.[4] An aging population, combined with improvements in cardiovascular event survival, has contributed to the rising prevalence and incidence of HF.[5]

Current Practice

ACEIs and beta-blockers are recommended in all patients with HF as they reduce morbidity and mortality.[1,4,6] Spironolactone has shown similar benefits but only in patients with severe HF.[4] Diuretics are used to alleviate symptoms in selected patients while digoxin may improve symptoms and reduce hospitalizations.[4,7]

Administration and Cost

Whereas dosing in hypertension is established, the optimal dosage of ARBs in HF is still not well defined. Losartan titrated to 50 mg once daily[8] and valsartan titrated to 160 mg twice daily[9] have been studied in long-term trials. These dosing regimens translate into daily drug costs ranging from $1.16 to $2.22. In comparison, a regimen of the ACEI captopril at 50 mg three times per day costs $1.68, using a generic product.[10]

Rate of Technology Diffusion

Consensus guidelines for HF currently recommend the use of ARBs as an alternative to ACEIs in patients who cannot tolerate ACEIs due to cough.[4] Whether ARBs will be recommended as a replacement for ACEIs or as an adjunct to current therapy, will be clarified as clinical and economic evidence accumulates.

Concurrent Developments

A new ARB, olmesartan medoxomil, has recently been approved in the US by the FDA but for the treatment of hypertension only.[11] Various neurohormonal pathways and peptides such as neutral endopeptidase, endothelin-1, aldosterone and cytokines (e.g. tumour necrosis factor) are currently being explored for potential drug development for the treatment of HF.[12]

The Evidence

A recent meta-analysis combined data on all-cause mortality and HF-related hospitalizations from 17 clinical trials.[13] Most of the included trials assessed short-term endpoints such as ejection fraction and exercise tolerance. In total, 12,469 patients and five ARBs (candesartan, eprosartan, irbesartan, losartan and valsartan) were tested, assuming a class effect for all ARBs. The results indicate that ARBs are not superior to ACEIs in reducing all-cause mortality or hospitalization in patients with HF. Combination therapy of an ARB and an ACEI carries the potential for additional benefits in terms of reduced hospitalization, but not mortality.[13]

The first long-term study (48 weeks) was the Evaluation of Losartan in the Elderly (ELITE) trial.[14] This study had originally been designed to compare the renal tolerance of losartan and captopril in 722 elderly patients with HF. However, a statistically significant reduction in all-cause mortality was observed in patients using losartan. In order to further investigate this possible effect, another study (ELITE II) was conducted.

The Losartan Heart Failure Survival Study (ELITE II) was designed similarly to ELITE but with sufficient power to determine whether a survival benefit of losartan over captopril truly exists.[8] A total of 3,152 ACEI naïve patients were randomized to either losartan or captopril with a mean follow-up period of 1.5 years. The primary endpoint was all-cause mortality and the secondary endpoint was a composite of sudden cardiac death or resuscitated cardiac arrest. In contrast to ELITE, no significant differences were found in the primary endpoint between the losartan group (280 deaths, 17.7%) and the captopril group (250 deaths, 15.9%) [hazard ratio (HR)=1.13 (95.7% confidence interval (CI): 0.95, 1.35)] or in the composite secondary endpoint [losartan 9.0% versus captopril 7.3%; HR=1.25, (95% CI: 0.98, 1.60)].[8] Losartan was generally better tolerated than captopril but the results failed to show the superiority of losartan compared to captopril in terms of mortality. The non-superiority of losartan should not be interpreted as equivalence to captopril as this study was not designed to test equivalency or non-inferiority.

The hypothesis that ARBs may provide additional benefit when combined with ACEIs and other conventional HF therapies was investigated in a number of short-term outcome trials.[13] Among these, the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study had the longest analytic horizon (43 weeks) and investigated the effects of candesartan on physiological outcomes (i.e. exercise tolerance).[15] This randomized, double-blind study had three treatment arms, candesartan alone, candesartan plus the ACEI enalapril, or enalapril

alone. The combination of candesartan and enalapril appeared to be more beneficial for preventing left ventricular dilatation and suppressing neurohormonal activation than either candesartan or enalapril alone.[15]

The Valsartan Heart Failure Trial (Val-HeFT) was the first study designed to measure morbidity and mortality in patients receiving an ARB combined with conventional HF therapy.[9] It was a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of adding valsartan to conventional therapy in 5,010 patients with HF. The two primary endpoints were all-cause mortality and the combined endpoint of all-cause mortality and morbidity. At baseline, 93% of all patients were receiving an ACEI and 35% were on a beta-blocker. At a mean follow-up period of 23 months, no significant difference was observed in all-cause mortality between the valsartan group (495 deaths, 19.7%) and the control group (484 deaths, 19.4%) [relative risk (RR)=1.02; (98% CI: 0.88, 1.18)]. The combined endpoint of mortality and morbidity was however significantly reduced among patients receiving valsartan (723 events, 28.8%) compared to the control group (801 events, 32.1%) [RR=0.87 (97.5% CI: 0.77, 0.97)].[9] However, the FDA determined this effect was largely driven by the 7% of patients not receiving an ACEI [HR: 0.51 (95% CI: 0.35, 0.73)], compared to patients using such therapy [HR: 0.92 (95% CI: 0.82, 1.02)].[2] Furthermore, the modest favourable trend in the group receiving an ACEI was mainly derived from the patients receiving less than the recommended dose of an ACEI.[2]

A *post hoc* subgroup analysis of the Val-HeFT trial found that within the 1,610 patients treated with both an ACEI and a beta-blocker at baseline, the addition of valsartan was associated with an increase in mortality (p=0.009) and a nearly significant increase in the combined endpoint of mortality and morbidity (p=0.10).[9] It is not known if this is a reproducible effect or a chance occurrence.[2]

Adverse Effects

Dizziness and hypotension are the most frequently reported adverse effects associated with ARBs at a rate similar to that of ACE inhibitors.[16] Clinical trials have shown that losartan is better tolerated than captopril with fewer patients discontinuing therapy due to side effects.[8,14] The incidence of cough and angioedema with ARBs have been observed to be similar to placebo in many studies.[16]

Implementation Issues

Further studies will be required to confirm whether ARBs are in fact equivalent to ACEIs and whether the combination of an ARB and an ACEI carries additional benefit or harm, compared to either agent used alone in the treatment of HF. These studies will also better define the population to be targeted.

Two long-term trials are currently ongoing, but their results are not expected to be available before 2003. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial is evaluating the role of candesartan in a broad spectrum of patients with HF (i.e. intolerant of ACEIs, with or without systolic dysfunction),[17] whereas the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) study is comparing irbesartan with placebo in HF patients with preserved left ventricular function.[18]

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