Intern Emerg Med (2011) 6:453–454
DOI 10.1007/s11739-011-0661-0

CE-THE CUTTING EDGE: RESEARCH UPDATE

Eplerenone, an aldosterone antagonist, reduces hospitalization and death in heart failure patients with nyha class II and an ejection fraction of less than 30%

Simone Birocchi · Giulia Carla Luisa Cernuschi · Gruppo di Autoformazione Metodologica (GrAM)

Received: 24 May 2011 / Accepted: 21 June 2011 / Published online: 17 July 2011
© SIMI 2011

Background

The renin-angiotensin-aldosterone system (RAAS) plays an important role in pathophysiology of heart failure (HF). RAAS blockade with angiotensin converting (ACE) inhibitor slows the progression of HF and improves the survival [1]. However, ACE inhibitors do not block the mineralocorticoid receptors, which are usually over expressed in patients with heart failure, and promote cardiac fibrosis in experimental models [2]. The latter has been confirmed by clinical trials that show a reduction in mortality and hospitalization of patients with severe heart failure in New York Heart Association class III–IV (NYHA III–IV) treated with spironolactone [3], or in patients after a myocardial infarction complicated by a reduced systolic function treated with eplerenone [4].

Thus, it is reasonable to suppose that the use of aldosterone antagonists might also delay the progression of heart failure in patients with mild failure symptoms (NYHA II).

Summary

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial [5] randomized 2,737 patients aged more than 55 years with NYHA II heart failure and an ejection fraction of not more than 35%, to receive either eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure. Death and hospitalization for any cause were secondary outcomes.

The trial was planned to last 48 months, but it was stopped prematurely, after a median follow-up period of 21 months, because of an overwhelming benefit in the eplerenone group. The primary outcome occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (hazard ratio, 0.63, 95% confidence interval (CI), 0.54–0.74, $P < 0.001$). A total of 12.5% of patients receiving eplerenone and 15.5% of those receiving placebo died (hazard ratio, 0.76, 95% CI, 0.62–0.93, $P = 0.008$); hospitalizations for heart failure and any other cause were also reduced with eplerenone. Among adverse events, only hyperkalemia showed a significant difference between the two groups: serum potassium level exceeding 5.5 mmol per litre occurred in 11.8% of patients in the eplerenone group and in 7.2% of those in the placebo group ($P < 0.001$). The estimated number of patients who would need to be treated to prevent one primary outcome per year was 19 (95% CI 15–27), and the estimated number needed to treat to postpone one death per year, was 51 (95% CI 32–180).

Strength of the study

- It addresses a relevant clinical issue (it's the first trial conducted among the patients in class NYHA II).
- Rationale of the study: there is a strong pathophysiologic background for the utility of aldosterone antagonists in heart failure patients, and the previous study already confirms this observation [3, 4];

S. Birocchi and G. C. L. Cernuschi on behalf of Gruppo di Autoformazione Metodologica (GrAM)

S. Birocchi (✉) · G. C. L. Cernuschi
Medicina Interna 2, Ospedale L. Sacco, Università degli Studi di Milano, Via G.B. Grassi, 74, 20157 Milan, MI, Italy
e-mail: simone.birocchi@studenti.unimi.it

- Good internal validity: it is a well-designed double-blind randomized controlled trial.
- The results are coherent and consistent (all the primary and secondary endpoints show a significant difference, and are consistent to one another.

Weakness of the study

- The trial was stopped early because of the net benefit of eplerenone therapy; this exposes the trial to a risk of bias, probably showing unreliable results, even if the stopping rule was preplanned [6].
- External validity: similar to previous studies on heart failure and as underlined by the authors, the population included in EMPHASIS-HF trial does not reflect the spectrum of patients with chronic heart failure met in common clinical practice. In particular there was a strong male gender prevalence (77.3% in eplerenone and 78.1% in placebo groups) and median age of about 69 years. In daily practice heart failure epidemiology is different, with older patients and more common in female gender [7].

Sponsorship

- It is a sponsored trial, and the sponsor collected, managed and analysed the data while an academic committee verified all the data.

Questionmarks

- Hyperkalemia was not a relevant problem in this study, as in the RALES trial [3], however, it is important to note that after the publication of the positive results of RALES, observational studies [8] show that the growth in the number of prescriptions of spironolactone coincide with an increase in the number of hospital admissions, morbidity and mortality related to hyperkalemia. This evidence suggests that the monitoring performed in the trial (i.e. for serum potassium) may lead to an underestimation of the occurrence of serious adverse events in clinical practice when the drug is administered to a wider population in a less controlled setting.
- The number of patients who withdrew from the study for an adverse event is quite high (13.8% in eplerenone and 16.2% in placebo groups), but the reason for the withdrawal is reported only in 1.5% of patients in eplerenone group and 1.8% in the placebo one.
- As eplerenone and spironolactone compete for the same mineralocorticoid receptor with aldosterone, it may be reasonable to hypothesize the same clinical effect. However, there is a marked difference in the cost between the two drugs.

Clinical bottomline

Aldosterone antagonists should be considered for the therapy of mild symptomatic systolic heart failure (NYHA class II) in addition to the recommended therapy. Close monitoring of the serum potassium concentration is mandatory during the treatment for the possibility of the occurrence of severe hyperkalemia, particularly in older patients with worse HF and concomitant ACE inhibitor therapy.

Conflict of interest None.

References

1. Pfeffer MA, Braunwald E, Moye LA et al (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. N Engl J Med 327:669–677
2. Weber KT (1999) Aldosterone and spironolactone in heart failure. N Engl J Med 341:753–755
3. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 341:709–717
4. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M (2003) Eplerenone, A selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 348:1309–1321
5. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B (2011) Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 364:11–21
6. Gordon Guyatt, Drummond Rennie, Maureen O. Meade, and Deborah J. Cook. Advanced topics in the validity of therapy trials, chapter 9.3
7. Costantino G, Rusconi AM, Duca PG, Guzzetti S, Bossi I, Del Medico M, Pisano G, Bulgheroni M, Solbiati M, Furlan R, Montano N (2009) Eligibility criteria in heart failure randomized controlled trials: a gap between evidence and clinical practice. Intern Emerg Med 4(2):117–122
8. Juurlink ND, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA (2004) Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med 351:543–551