Challenges in trials evaluating statins in heart failure

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Abstract

It is proving exceedingly difficult for novel therapeutic agents to demonstrate clinical benefit additional to standard medications in patients with established chronic heart failure. Despite this, HMG CoA reductase inhibitors (statins) are being extensively evaluated for just such an indication. Challenges in conducting clinical studies in this area relate primarily to the design of trials to maximise the possibility of a beneficial effect being demonstrated, if indeed one exists. The patient population studied, eg. ischaemic versus idiopathic etiology, as well as severity of disease being evaluated are such potential challenges. Other issues relate to the drugs being studied; whether statins can be considered an exchangeable drug class and the dose of drug being studied. Finally, choice of clinical endpoints to maximise the chances of a favourable outcome add further complexity. All of the above challenges faced the recently published Conrolled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study of rosuvastatin in patients with ischaemic heart failure as well as the ongoing Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardio (GISSI-HF) study of both ischaemic and idiopathic dilated cardiomyopathy.

Key words: statins, heart failure, clinical trials.

Introduction

Novel therapeutic interventions in trials of patients with heart failure have had a major challenge in demonstrating efficacy, above and beyond standard therapies. This has been well demonstrated in trials of a number of seemingly promising therapeutic strategies (Table I) including endothelin receptor antagonists [1], tumour necrosis factor TNF-α inhibitors [2] and vasopeptidase inhibitors [3]. Recently, long-term therapy with a vasopressin antagonist has also been unsuccessful [4].

These neutral findings may represent a combination of a number of factors:

- the patient population being studied may be inappropriate for the therapy being studied;

Table I.

Trial	Drug	Mechanism of action
RENEWAL	Etanercept	TNF blockade
ENABLE	Bosentan	Endothelin blockade
OVERTURE	Omapatrilat	Vasopeptidase inhibition
EVEREST	Tolvaptan	Vasopressin V2 antagonism

- the mechanistic hypothesis being tested may be incorrect;
- the endpoint evaluation not appropriate for the therapy being studied;
- a threshold for pharmacological benefit may have been reached with existing therapies.

All of the above considerations are highly relevant to the assessment of statin therapy for the treatment of chronic heart failure, additional to standard management strategies including blockade of the renin-angiotensin-aldosterone and sympathetic nervous systems.

Patient population

Ischaemic verus idiopathic etiology

One of the major challenges in trials testing heart failure strategies is the patient population being studied.

Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) [5] specifically studied patients with an ischaemic etiology of their heart failure because they were formally testing the hypothesis that by reducing ischaemic events that would translate into a reduction in not only fatal myocardial infarctions (MIs) and strokes but also in progression of the heart failure disease process as well as a reduction in sudden death. This last concept is supported by autopsy findings of the Assessment of Treatment with Lisinopril and Survival (ATLAS) study of high-dose vs. low dose lisinopril in patients with systolic heart failure [6]. A substudy of ATLAS showed that a high proportion of those with so-called sudden death manifested an acute coronary event on autopsy.

Patients with idiopathic dilated cardiomyopathy as the etiology of their heart failure may also benefit from the pleotropic, ie. cholesterol-lowering-independent effects, of statins. These include a number of pharmacological actions discussed at length in other manuscripts in this issue of Archives of Medical Science such as anti-inflammatory effects, beneficial autonomic effects, anti-fibrotic effects and reduction in RhoA/Rho-kinase system activation [7].

Against the above potential benefits of statins, have to be weighed the potential for adverse effects, which have also been extensively covered elsewhere in this issue. Briefly, these include:

(i) the so-called "reverse epidemiology" of lipid levels and clinical outcomes in patients with established heart failure (ie. patients with the lowest cholesterol levels are those with the highest cardiovascular (CV) event rate) [8];

(ii) the endotoxin-lipoprotein hypothesis, suggesting that lower lipoprotein levels reduce the body's ability to mop up lipopolysaccharide which is introduced via the gut in the setting of heart failure-associated gut oedema [9];

(iii) reduction in Coenzyme Q10 levels [10], observed with statins across a variety of patient disease states, and which in the heart failure context may adversely influence myocyte function.

A critical factor in the selection of patients according to disease etiology is the known beneficial effects of statins in primary and secondary prevention of coronary artery disease and atherosclerosis. Therefore, many countries invited to participate in CORONA (e.g. Australia, Canada, USA) declined because it was felt unethical to deprive patients with an ischaemic etiology of their heart failure (especially those with proven myocardial infarction) the potential for secondary prevention benefits. The counter argument against this is that in the heart failure setting clinical equipoise is greater with these agents than in other ischaemic settings, for the reasons mentioned earlier. For this reason, we had great difficulty recruiting ischaemic patients into our RosUvastatiN Impact on VEntricular Remodeling, LipidS and CytokinEs (UNIVERSE) study of rosuvastatin in chronic heart failure (CHF) [11], where both ischaemic and idiopathic etiologies were permitted. Indeed, we ended up with approximately 90% of patients enrolled being of an idiopathic etiology. It would be of great interest to see whether this same ratio holds true in the GISSI-HF [12] study which is ongoing and also permits entry to patients of ischaemic and non-ischaemic etiologies.

Severity of disease

Selection of patients with the appropriate disease severity to benefit from a specific intervention is emerging as a critical factor in the success of trials of new agents in heart failure. For example, one potential reason for the lack of success of TNF-α receptor antagonists in heart failure is that the major outcome studies [2] were in "all comers" with a broad range of symptom severity rather than those most likely to benefit from this specific therapeutic strategy, such as those with the most activated TNF-α systems.

In the context of statin therapy, the issue therefore arises as to what severity of disease is most likely to be benefited from statin therapy. The recent CORONA [5] study recruited patients with more advanced heart failure than other "all comer" studies, perhaps because of the ejection fraction requirement being stricter in Class II patients. It has therefore been suggested that the neutral results observed in CORONA may have been as a result of this advanced patient disease severity. Specifically, the proposition has been put forward that these ischaemic patients were "too far gone" to benefit from the pleotropic effects of statins on a scarred, poorly functioning ventricle.

There are, however, arguments against this hypothesis. Firstly, when patients were looked at in

subgroups in CORONA according to New York Heart Association Class, ejection fraction level and other markers of disease severity, no heterogeneity in these responses was observed. Furthermore, other agents such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and in particular aldosterone antagonists, have all been shown to exert beneficial effects even in patients with the most advanced disease.

CORONA patients were also older and it has been argued that many were "too old" to benefit. Again, however, other classes of agents have been shown to remain effective in the elderly.

Drug

Drug class

All drugs within a drug class should be considered on their individual merits, both with regard to efficacy and to adverse effects [13]. The issue arises in the context of trials of statins in heart failure as to whether there is any one drug within the statin class that may be preferred.

The answer appears to be that all statins seem equally likely (or unlikely) to benefit patients with heart failure based on the range of differing drugs used in pre-clinical studies and in small, prospective mechanistic type trials. These latter trials have included atorvastatin [14], simvastatin [15] and rosuvastatin [11]. Therefore, the pharmacological differences between agents in the statin class do not appear to be relevant to the mechanistic benefits observed in these studies. It has been pointed out that both the UNIVERSE study of 40 mg of rosuvastatin [11] and the CORONA study of 10 mg of rosuvastatin [5] were both neutral studies raising the possibility that it is rosuvastatin that is responsible for this neutrality. However, rosuvastatin has been clearly demonstrated to have a beneficial remodelling effect in a recently published animal model study [16].

The same considerations apply with regard to tolerability, safety and adverse event profile. With the notable exception of cerivastatin (since withdrawn), these agents demonstrate remarkable consistency with regard to their adverse event and tolerability profile. This was underlined by the results of CORONA in which, despite the advanced age and disease severity of the patient population studied, 10 mg of rosuvastatin was not associated with any increase in adverse event profile compared to placebo over a prolonged exposure period.

Drug dose

Differential effects of drugs at different doses is one of the most controversial areas in clinical pharmacology and therapeutics. There are many examples of drugs having effects at one dose which are negated at differing doses or even begin tracking in an opposing direction. Therefore, what is occurring at a certain dose may not necessarily be doing so at others. Furthermore, patients have pharmocogenomic differences in drug handling and this may result in differing plasma and tissue concentrations of individual drugs despite identical doses being administered orally.

All of these considerations are by way of background to the context of statin therapy and dose in the treatment of heart failure. This area remains contentious. In the UNIVERSE study of 40 mg rosuvastatin [11] a neutral impact on ventricular remodelling was observed. Interestingly, the Bleske study of high-dose atorvastatin (80 mg/day) [17] similarly observed a neutral effect on inflammatory markers and neurohormonal parameters. However, this was a small study involving only 15 patients in a cross-over trial design.

Given both the favourable and potentially unfavourable effects of statins, specifically in the heart failure context, this does raise the hypothesis that at higher statin doses the unfavourable effects began to outweigh the favourable leading to a neutral result. However, the recent TNT study would somewhat argue against this. Analysis of patients who developed heart failure during this study of a coronary artery disease population [18], clearly noted more favourable outcomes at the high dose of atorvastatin 80 mg than the lower dose of 10 mg. Against this, this was not a patient population with current heart failure on study entry. Therefore, this issue remains contentious.

Endpoint evaluation

Critical to the success of any trial is choosing the right endpoints to match the known mode of action of the drug and the expectation of where the clinical benefit may be most likely to be observed.

This was recently fine-tuned in the CORONA study [5] where the expectation was that the anti-ischaemic effects of rosuvastatin in a 100% ischaemic population may be paramount. Therefore, the study investigators did not use the conventional heart failure clinical endpoint of some combination of death and (heart failure or cardiovascular) hospitalisation. Rather, CORONA included fatal strokes and fatal MIs in its primary endpoint evaluation. Interestingly, despite tweaking the primary endpoint towards that where the greatest benefits may be expected, a neutral result was still observed.

The same issue holds true even for smaller mechanistic studies. A primary endpoint must be declared in any sample size calculation to adequately size the study and therefore the endpoint of greatest interest or greatest likelihood of success with the intervention is normally declared as the primary or co-primary endpoint. In UNIVERSE [11], left ventricular

remodelling as assessed by radionucleotide ventriculogram was that primary endpoint. It was chosen because it provided a reproducible measure of left ventricular ejection fraction that could be readily calculated in the exact same manner for all studies in a core laboratory. Its reproducibility is excellent and is certainly more precise in evaluation of ejection fraction than echocardiography. This allowed us to size the study for a relatively modest number of patients to demonstrate a 3% absolute ejection fraction improvement which was both statistically relevant and clinically meaningful. Interestingly, the 3% improvement was indeed observed, however, there was a similar (if not greater) placebo response which completely neutralised any treatment effect. This placebo improvement was unexpected, appeared to be unrelated to post randomisation addition of other therapies and remains to this day unexplained. However it was enough to completely negate any putative benefit of statin on remodelling. In support of these findings, an accompanying echocardiographic study of the same patients, albeit not analysed in a core laboratory, also demonstrated very similar observations with regard to a placebo improvement in ejection fraction and ventricular dimensions.

Summary and conclusions

As with all studies these days of new therapies for chronic heart failure a series of potential minefields need to be negotiated before a successful outcome can be arrived at.

As has been explained in detail, considerations such as the etiology of the patient's heart failure, the severity of the patient's disease, the drug (and dose) being studied and the endpoint evaluation as well as analytical approach all have the potential to result in a study not deviating sufficiently from neutrality. Of course, statins are not alone with regard to these considerations and this has resulted in at least 4 promising classes of drugs not being able to demonstrate benefit over and above standard heart failure therapies. However, this is even more of an issue with statin therapies where the well known potential adverse effects of these agents in the heart failure setting perhaps add to the difficulty in achieving a significant positive outcome.

Nevertheless, despite these difficulties, we are still not at the end of the statin story in heart failure. GISSI-HF [12] is probably our last "role of the dice" with regard to demonstrating these agents as being beneficial in this setting. However, GISSI-HF itself has a number of complexities to it which may work against the success of statins in this study. The first is that not only systolic but also diastolic heart failure patients will be included. The literature supporting a beneficial effect of statins in diastolic heart failure is weak, however may be mechanistically plausible as in systolic heart failure. Secondly, the statin is being given as part of a 2×2 factorial design with the other intervention being polyunsaturated fatty acids (PUFAs). Because there are overlapping mechanisms of action between PUFAs and statins it may be that benefits will be less than additive again tending to neutralise the result versus placebo. Nevertheless, despite these difficulties, the results of GISSI-HF are eagerly awaited.

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