Angiotensin converting enzyme inhibitors and angiotensin receptor (AT1) antagonists: either or both for primary renal disease?

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Introduction

The activity of the Renin-Angiotensin System (RAS) may contribute to progression of renal diseases as a result of its effect on arterial blood pressure and intraglomerular pressure. In addition, there is evidence that RAS may also act via non-haemodynamic mechanisms such as mesangial cell mitogenesis and by influencing the balance of accumulation and degradation of extracellular matrix in mesangial cells and interstitium which may contribute to the development of glomerulosclerosis [1,2]. The benefits of reducing RAS activity in patients with diabetic nephropathy and non-diabetic renal disease have been demonstrated in prospective trials in which angiotensin-I-converting enzyme inhibitors (ACEI) were shown to have a renoprotective effect greater than that afforded by strict blood pressure control alone [3,4]. With the introduction of angiotensin II receptor antagonists (AT₁-ra), there is now a choice as to the method of RAS manipulation and recent editorials in this journal have reviewed the role of the RAS within the kidney and highlighted some of the similarities and differences.

References

between ACEI and AT1-ra [5–7]. We would like to add to the debate regarding the merits, or otherwise, of these drugs in clinical practice and highlight the potential role of molecular biology in future clinical decision making.

**Limitations of ACE inhibition**

ACE is not specific to the RAS and is involved in the breakdown of several other products, such as bradykinin. Elevated levels of bradykinin is probably the mechanism for the ACEI-related side effects such as cough and anaphalactoid reactions [8]. Cough occurs no more frequently with AT1-ra than with placebo [9]. While ACE is the principal method by which angiotensin I (A1) is converted to angiotensin II (AII), this step can also be carried out by other enzymes. Non-ACE formation of AII is not blocked by ACEI and may be important in maintaining tissue AII levels. In the heart, for example, cardiac chymase activity contributes to formation of AII and is unaltered by ACEI. Indeed, the effect of the non-ACE pathways may actually be exaggerated during treatment with ACEI as a result of high levels of AII and AT1 receptor up-regulation. It is not clear, however, if the non-ACE conversion of AII to AII is of clinical significance although there is evidence that all levels gradually rise with time after starting ACEI [10]. AT1-ra, by contrast, offer the possibility of ‘total blockade’ of the effects of AII at the AT1 receptor that cannot be achieved by ACEI.

**Limitations of AT1 receptor blockade**

The results of prospective clinical trials evaluating the role of AT1-ra in renal disease are not yet available and their efficacy, in this respect, remains unproven. Similarities in the mode of action (i.e. reduced AII-mediated activity) of AT1-ra and ACEI may suggest that their clinical effects will be comparable. There are several reasons, however, why this may not be the case. In rats the beneficial effect of ACEI on renal haemodynamics is partly through bradykinin-mediated dilatation of the efferent arteriole [11]. This accounts for the fall in intraglomerular pressure (and the initial fall in glomerular filtration rate [GFR] and protein excretion [12]) after ACEI. In animal models AT1-ra do not appear to produce the fall in proteinuria that is observed with ACEI although they have a similar effect on the attenuation of glomerulosclerosis [13]. In the absence of salt and water depletion, AT1-ra do not have this acute haemodynamic effect on the human kidney and do not produce an initial fall in GFR [14,15]. A study of 13 patients did, however, observe a reduction in proteinuria with AT1-ra despite no change in GFR [14]. The relative contribution of haemodynamic and non-haemodynamic mechanisms to the renoprotective effect of ACEI is not known, although the reduction in proteinuria appears to correlate with the degree of attenuation of GFR reduction. Increased bradykinin levels may also have important non-haemodynamic benefits by increasing the activity of metalloproteases which degrade extracellular matrix.

In addition to actions on AT1 receptors, AII also stimulates AT2 receptors. It may be premature to speculate on the importance of AT2 receptor stimulation as their clinical role in healthy humans and disease states has not been fully elucidated. In healthy humans AT2 receptor expression in the kidney appears to be low. Stimulation of these receptors does, however, appear to have an effect of lowering blood pressure (possibly by a central mechanism involving reduction in sympathetic nervous system activity) which may contribute to the antihypertensive effect of AT1-ra. This dual antihypertensive action may limit the dose of AT1-ra such that maximally tolerated doses (as judged by blood pressure response) may be below the doses required to produce additional renoprotection (resulting from blockade of the ‘local’ RAS). Within the kidney AT2 stimulation has an antinatriuretic effect and may reduce degradation of extracellular matrix leading to accumulation in the glomerulus [7,16]. The local effect of AT1-ra is dependent upon the distribution of AII receptor subtypes and considerable interspecies variation in distribution has been demonstrated [17]. As a consequence of this the effects of AT1-ra seen in animal studies, e.g. regression of left ventricular hypertrophy [18], may be more difficult to demonstrate in humans as a result of the increased expression of AT2 receptors in human myocardium [19,17].

**ACEI and AT1-ra alone or in combination?**

AT1-ra should not be seen solely as an alternative to ACEI. Some patients do not achieve satisfactory blood pressure control (or renoprotection) on maximal doses of ACEI and the combination may, therefore, allow further RAS blockade while overcoming some of the concerns of using either agent in isolation. Additional RAS blockade has been confirmed by a further increase in plasma renin levels [20] and seems not to have adverse clinical or biochemical effects. Animal models, however, have not found the combination to be better than either drug alone [21]. Further work is required to study the expression of AT1 receptor in disease states and to examine the possibility that some of the actions of AT1-ra may be due to AT2 receptor stimulation. If the actions of AT1-ra were found to be mediated partly by AT2 receptor stimulation then the reduction in angiotensin II levels caused by ACEI may be a possible explanation for the failure to demonstrate clinical synergy by concomitant use of both agents.

**Trials involving AT1 receptor antagonists**

A recently published trial comparing AT1-ra and ACEI in patients with cardiac failure [ELITE] suggested that...
AT1-ra are better tolerated [22]. There was also a suggestion of superior efficacy of AT1-ra although this may be explained partly by a difference in compliance if ACEI were associated with increased side-effects. A study on the effect of AT1-ra on cardiovascular end-points is underway (Losartan Intervention for Endpoint Reduction—LIFE) as are separate studies into the effects of Ibersartan (by the Collaborative Trial Group) and Ibersartan (the RENAAL study) in delaying progression to end-stage renal failure in patients with type II diabetes and established nephropathy. The Ibersartan and the Losartan studies will also evaluate the effect of AT1-ra on cardiovascular events in a group at high risk of developing cardiovascular complications but they do not consider the effect of preventing the progression from microalbuminuria to overt nephropathy, as was shown recently for ACEI [23]. Unless trials directly comparing AT1-ra to ACEI (± combined treatment) are carried out, the indication for AT1-ra over ACEI, with the exception of intolerance to the latter, will remain elusive.

The role of molecular biology

Factors influencing RAS activity may determine the rate of progression of renal disease. RAS activity is under genetic control and some studies have suggested an effect of polymorphisms of the angiotensinogen and ACE genes on the rate of progression of diabetic and non-diabetic renal disease [24–28] while others have failed to observe such an effect. Additionally, there is some evidence that ACE genotype may influence response to treatment with ACEI [29]. Organisers of AT1-ra studies have an ideal opportunity to incorporate molecular biology into their overall design. Studies of this size could provide a great deal of information in terms of identifying factors related to disease progression and therapeutic response to AT1-ra. Most studies involving the genetic polymorphisms of RAS components are retrospective and non-interventional and studies of this size and design are urgently needed. Polymorphisms of the AT1 receptor gene have been described and, although they have not been extensively studied, synergy between these and polymorphisms of the ACE gene on the risk of myocardial infarction has been suggested [30]. Thus, if information was available as to the natural history of disease and response to treatment as a function of genotype, it may be possible to predict individual patient response to RAS blockade at various points, such that a choice between ACEI and AT1-ra (neither or both) could be made.

Summary

At the present time we cannot assume that the proven benefits of ACEI on renal disease will be reproduced by using AT1-ra. With potentially differing modes of activity of these drugs, they cannot be seen as interchangeable and ACEI should remain the drug of choice in patients with progressive renal disease unless they are not tolerated. It is possible that AT1-ra may offer additional advantages in some patients or that synergy exists between the two agents, but this view will remain entirely speculative unless proper trials are conducted. Despite the results of the ELITE study [22], the uncertainty regarding the use AT1-ra in cardiovascular disease mirrors that of renal disease. This issue is obviously of relevance to the nephrologist in view of the spectrum of cardiac disease that accompanies chronic renal failure, such as left ventricular hypertrophy and cardiac failure, which provide multiple indications for manipulation of RAS. Despite their renoprotective effect, previous studies on ACEI [3,4] have not shown an overall reduction in mortality and this issue needs to be addressed in addition to renoprotection in studies comparing AT1-ra and ACEI.

References

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