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Between-patient differences in the renal response to renin-angiotensin system intervention: clue to optimising renoprotective therapy?

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Abstract

Renin-angiotensin-aldosterone system (RAAS) blockade with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II (Ang II), AT_1-receptor blockers (ARB) is the cornerstone of renoprotective therapy. Still, the number of patients with end-stage renal disease is increasing worldwide, prompting the search for improved renoprotective strategies.

In spite of proven efficacy at group level, the long-term renoprotective effect of RAAS blockade displays a marked between-patient heterogeneity, which is closely linked to between-patient differences in the intermediate parameters of blood pressure, proteinuria and renal haemodynamics. Of note, the between-patient differences by far exceed the between-regimen differences, and thus may provide a novel target for exploration and intervention.

The responsiveness to RAAS blockade appears to be an individual characteristic – as demonstrated by studies applying a rotation-schedule design. The type and severity of renal disease, obesity, insulin-resistance, glycaemic control, and genetic factors may all be involved in individual differences in responsiveness, as well as dietary factors, such as dietary sodium and protein intake.

Several strategies, such as dietary sodium restriction and diuretic therapy, dose-titration for proteinuria, and dual RAAS blockade with ACE-I and ARB, can improve the response to therapy at a group level. However, when analysed for their effect in individuals, it appears that these measures do not allow poor responders to catch up with the good responders, i.e. in spite of their efficacy at group level, the available measures are usually not sufficient to overcome individual resistance to RAAS blockade.

We conclude that between-patient differences in responsiveness to renoprotective intervention should get specific attention as a target for intervention. Unravelling of the underlying mechanisms may allow development of specific intervention. Based on the currently available data, we propose that response-based treatment schedules, with a multidrug approach titrated and adapted at individual responses rather than fixed treatment schedules, may provide a fruitful strategy for more effective renoprotection.

Introduction

Antihypertensive drugs interrupting the renin-angiotensin-aldosterone system (RAAS) provide important tools to slow the progressive course of chronic renal disease. Their specific renal effects distinguish the angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II (Ang II), AT_1-receptor blockers (ARB) from other antihypertensives. Both classes reduce intraglomerular pressure (by limiting Ang II-induced efferent vasoconstriction) and lower proteinuria. Because their effects appear to go beyond mere blood pressure (BP) control, RAAS blockade has become the cornerstone of renoprotective therapy.[1-5]

Despite the improved therapeutic armamentarium, however, the number of patients with end-stage renal disease (ESRD) is increasing worldwide, and improvement of therapeutic strategies is urgently required. Whereas the renoprotective effects of ACE-I and ARB have been convincingly shown in several large trials, for individual patients the long-term renoprotective effect can range from a complete arrest of renal function loss to complete absence of response.

In this paper, therefore, we want to highlight the marked between-patient heterogeneity in response to RAAS blockade as a target for further exploration that may provide new strategies to improve renoprotection. We will discuss the alleged patient-related factors underlying this interindividual variability in the responses to RAAS blockade. The benefits and limitations of current strategies to improve the response to therapy are then reviewed for their potential to overcome individual resistance to therapy, and finally the implications for future strategies for improvement of renoprotective strategies will be set out.

Between-patient variability in response to RAAS blockade: rule rather than exception

Controlled, randomised trials are essentially designed to compare the efficacy of different regimens at a group level and, albeit the current gold standard for group data, individual factors are kept out of sight, being a potential source of bias controlled for by randomisation or stratification. As outlined below, shifting the focus towards an individual perspective, however, discloses that within-group (between-patient) differences in therapeutic benefit by far exceed the differences between treatment groups, which provides an obvious rationale for exploring the factors underlying individual differences in responsiveness.

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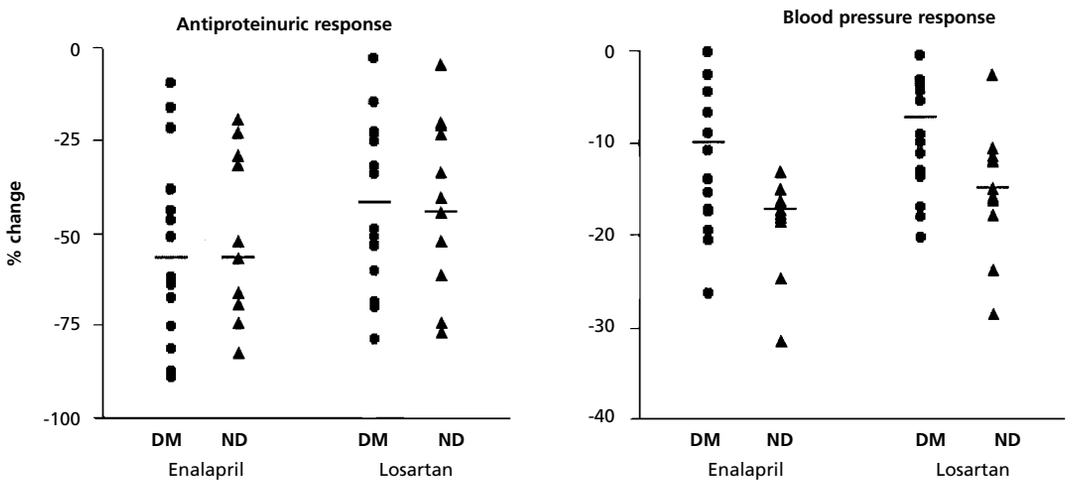
Figure 1 Individual responses of proteinuria (left panel) and mean arterial pressure (right panel) to a standard dose of RAAS blockade with ACE-I (enalapril 20 mg) or ARB (losartan 100 mg), in Type 1 diabetic (DM) and non-diabetic (ND) renal patients. Responses are calculated as % change from baseline period without therapy (Patient data from:[17])



A different design of studies, for example a rotation treatment design, allows one to address therapy-responsiveness as an individual patient characteristic. An elegant example of such an approach is provided by a crossover rotation study in essential hypertensive patients, testing four different classes of BP-lowering agents.[6] As expected, all classes of these registered antihypertensives were effective at a group level. However, some patients were particularly susceptible to ACE-I and beta blockade, while calcium channel blockers or diuretics were more effective in others. Thus, important information can be obtained by searching for individual response patterns – information that remains invisible by the traditional way of investigation.

As to renoprotection, not only the efficacy of long-term preservation of renal function varies widely between individuals, but also the responses of BP, proteinuria and renal haemodynamics. In this respect, it is important to note that, during antihypertensive treatment, the short-term responses of renal haemodynamics,[7] as well as proteinuria,[8,9] are predictive for the between-patient differences in long-term preservation of renal function. In other words, between-patient differences in short-term response parameters predict the between-patient differences in long-term renoprotection.

The predictive efficacy of the antiproteinuric response is consistent with a benefit derived from interrupting the tubular toxic effects of proteins leaked through the glomerular barrier[10] – i.e. with a causal role for reduction of proteinuria in long-term renoprotection.[11,12] Therefore, reduction of proteinuria is currently considered an independent therapeutic target.[13-16] For our present purpose, moreover, the short-term antiproteinuric response is a relevant parameter to explore the factors underlying between-patient differences in responsiveness to RAAS blockade.

The magnitude of the between-patient variability, even within the standardised setting of a clinical trial, is illustrated by the individual data from a previous study,[17] performed as a collaboration between Parving's group and our own, showing the responses to ACE-I and ARB in Type 1 diabetic and non-diabetic renal patients (Figure 1). As indicated by the median values, it is clear that both drugs effectively reduce proteinuria and BP at the group level. Nevertheless, in both the non-diabetic and the diabetic patients, the inter-individual variability in the responses of proteinuria and BP is striking, with the response of proteinuria, in particular, ranging from virtually zero to almost 100% reduction.

Possible causal factors in between-patient differences in responsiveness to RAAS blockade

Several causes may, independently or combined, contribute to between-patient differences in responsiveness to therapy, such as the type and severity of pre-treatment renal damage, obesity and insulin-resistance, and dietary and genetic factors. Some of these, particularly diet and obesity, are at least potentially modifiable and thus provide a target for intervention. Other factors, such as genetic make-up, cannot be modified at the current state of knowledge, but this should not lead to therapeutic nihilism. Identification of such factors can guide the unravelling of the underlying mechanisms of therapy resistance, and thus pave the way for improved therapy in a more indirect way.

Type and severity of renal disease

Whereas RAAS blockade is effective in chronic renal failure of diverse origin, there is nevertheless some evidence that the efficacy of renoprotective treatment is not similar for all renal disorders. For example, polycystic kidney disease shows faster progression during intervention[18] and nephropathy due to Type 2 diabetes seems less susceptible to ACE-I than Type 1 diabetic nephropathy (reviewed in[19]).

Nevertheless, it must be stressed that impressive between-patient differences are usually also

found within a given disease. Interestingly, a retrospective analysis showed that the antiproteinuric efficacy of ACE-I was inversely related to the extent of vascular and interstitial renal lesions in renal transplant recipients[20] and ACE-I efficacy also has been observed to be prevented by advanced (sclerotic) lesions of the glomerulus and/or thickening of the basement membrane, which could explain its poor effect in Type 2 diabetic nephropathy.[19] Both notions are in agreement with recent prospective findings in rats with established nephrosis, showing that the pre-treatment severity of both interstitial and glomerular renal lesions on renal biopsy predicted a poor antiproteinuric response and a poor histological outcome to ACE-I and ARB.[21]

Thus, antiproteinuric efficacy of treatment is apparently lower if structural damage is already advanced by the time treatment is started. If this holds true, the delay between the onset of disease and the start of treatment could partially explain interpatient variability in response to therapy, although this is obviously hard to prove in humans. Animal experiments, however, allow standardisation with respect to timing. A study in streptozotocin-diabetic rats indeed showed a better antiproteinuric response if ACE-I treatment was started early, as compared with late treatment.[22] Although it has become clear that it is never too late to start ACE-I,[23] the data summarised here also suggest that an early start is to be preferred.

Finally, recent experimental data suggest that the systemic sequelae of proteinuria, i.e. the severity of systemic nephrotic alterations, may adversely affect the efficacy of ACE-I, as in rats with severe, established nephrosis, the antiproteinuric response to ACE-I was not only predicted by the severity of pre-treatment proteinuria, but also independently by the concomitant severity of hypercholesterolaemia as an index of systemic nephrosis.[24] The absence of a predictive effect for the BP response suggests that the poor response in the severely nephrotic animals was not merely due to more severe volume expansion. However, whether the predictive effect of hypercholesterolaemia in this model reflects a true effect of hyperlipidaemia on responsiveness to ACE-I, or is just a marker of other features of nephrosis, such as coagulation disturbances or hypo-albuminaemia, remains to be investigated.

Dietary factors

Sodium status is an important determinant of the therapy response to RAAS blockade with respect to BP[25] and renal haemodynamics[26] as well as to proteinuria.[27] It is well established that these drugs are ineffective during states of volume excess, either due to renal dysfunction, to nephrotic syndrome, or simply due to ingesting excess sodium, which is reversible upon correction of the volume excess by sodium restriction,[25,27] and/or diuretic treatment.[28]

Protein intake is another source of dietary variation that can modify the response to RAAS blockade, as, in overtly nephrotic patients, the antiproteinuric efficacy of ACE-I is significantly enhanced by shifting from a normal to a low protein diet.[29] Thus, between-patient differences in dietary intake can be a major source of response variability.

Obesity, insulin resistance and glycaemic control

The role of obesity in renal disease has received relatively little attention.[30] However, it has been reported that the antiproteinuric effect of ACE-I fails to persist in obese proteinuric patients.[31] Also, as noted above, the antiproteinuric effect of ACE-I is relatively poor in Type 2 diabetic patients with nephropathy,[19] a patient category characterised by obesity and insulin resistance. On the other hand, in Type 2 diabetic patients who were sodium-depleted, the body mass index proved to be strongly related to the renal vasodilatory response to RAAS blockade with irbesartan.[32] Thus, obesity and/or insulin resistance may somehow modify the response to RAAS blockade.

One explanation might be insulin resistance-induced sodium-retention, which in turn impairs the efficacy of RAAS blockade.[33] On the other hand, adipose tissue itself is increasingly recognised as a metabolically active site, possibly also with effects on the kidney. For example, the adipocyte-derived hormone, leptin, the plasma levels of which are increased in obese subjects,[34] has the potential to induce TGF-β in glomerular endothelial cells[35] and has been proposed to play a role in progressive renal disease.[36] Moreover, adipose tissue appears to harbour a local renin-angiotensin system which is suggested to have consequences that surpass those of mere autocrine effects.[37]

In the diabetic population, glycaemic control could be another relevant factor. Interestingly, studies in sodium-replete healthy subjects have shown that a hyperglycaemic state increases renal plasma flow[38] and furthermore enhances the usual ACE-I[38] or ARB-induced[39] increase in renal plasma flow, suggesting an increased efferent vascular tone due to hyperglycaemia-induced intrarenal RAAS activation. In line with this, subjects with Type 1 diabetes mellitus display an exaggerative renal haemodynamic response to ACE-I and ARB[40] and abstract data suggest that this is even more pronounced in patients with poor metabolic control.[41] Taken together, these data suggest that glycaemic control may be a relevant factor to consider in between-patient variability in therapy response in diabetic patients.

Genetic factors

Interest in genetic determinants of drug efficacy ('pharmacogenomics') has considerably increased in recent years, fuelled by the developments in molecular genetic techniques.[42] Several years ago, ethnic differences in the BP response to ACE-I in hypertension already pointed towards a role of genetic factors in responsiveness to RAAS blockade.[43] A recent study, moreover, showed familial factors to be involved in the BP response to lisinopril, in a study in hypertensive sibling pairs.[44]

The search, however, for the specific genes involved in the response to RAAS blockade is complicated. It should be noted that the response to pharmacological intervention in multifactorial processes such as renal disease is determined by many factors, and thus should best be considered a complex phenotype. Variations in the direct molecular target of the drug action, as well as in underlying pathophysiological factors and in compensatory responses, each subject to genetic regulation as well as to environmental factors, may all be involved in the eventual therapeutic benefit.

For the response to RAAS blockade in renal patients, this would amount to many different candidate genes. Differences in the genetic make-up of the RAAS may be relevant (genetic polymorphisms for ACE, the AT_1-receptor, and angiotensinogen) but also genes involved in sodium handling and volume status, for example the polymorphisms of the adducin gene,[45] as well as genetic differences in compensatory responses, such as baroreflex sensitivity.[46,47]

To add to the complexity, more likely than not, these different potential factors may interact in various ways, depending on the specific pathophysiological context. So far, in renal patients, most attention has been focussed on ACE (I/D) polymorphism as a potential determinant of the response to ACE-I. This has an obvious rationale, considering the relationship between the number of D-alleles and plasma and tissue (and/or kidney) ACE levels.[48] At first glance, the data seem conflicting, as in DD homozygotes the antiproteinuric response to ACE-I has been reported to be similar, worse, or better than in subjects harbouring one or two I–alleles (reviewed in[49]). However, most data were obtained from relatively small *post hoc* studies, which hampers the assessment of potential interactions with other relevant genetic or environmental factors.

Data from the Ramipril Efficacy In Nephropathy (REIN) trial provided evidence for an interaction between ACE genotype, response to ACE-I and gender.[50] In a prospective study in healthy volunteers, we found that dietary sodium restriction obliterated the phenotypic characteristics of DD homozygotes, suggesting a gene-environment interaction between ACE genotype and sodium intake.[51] *Post hoc* data suggest that sodium intake may also be relevant to the impact of ACE genotype on therapy response in renal patients.[52]

Thus, several interactions demonstrate the need for well-controlled studies of sufficient size and power to further explore the genetic basis of differences in therapy response, based on taking proper account of interaction with other relevant genetic and environmental factors. This should provide an assessment of the relative impact of genetic versus phenotypic determinants of therapy response,[53] and identify the contextual factors (other genes, but also factors such as gender and sodium intake) that allow alleged candidate genes to exert effects on therapy response. Obviously, modifiable contextual factors (such as sodium intake) are of particular interest, as these may provide a tool to overcome the possible adverse effects of a specific genetic make-up on therapy responsiveness.

Optimising the response to RAAS blockade: from group data towards an individual perspective

Several pharmacological and non-pharmacological measures are available to optimise the efficacy of RAAS blockade, as outlined below. So far, however, these measures have been mainly evaluated by their effect at a group level. For our purpose, however, it would be important whether such measures diminish the differences between good and poor responders, to allow the poor responders to catch up with the good responders.

Dietary measures

Dietary measures of potential benefit to the renal patient include sodium restriction, protein restriction and reduction of body weight in obese patients. The rationale for these measures should clearly be considered from the perspective of overall risk reduction in the renal patient, but here we will only discuss the implications for therapy response.

In patients with obesity-related glomerulopathy, reduction of body weight can considerably reduce proteinuria,[54] but whether weight reduction might enhance the responsiveness to RAAS blockade, to the best of our knowledge, has not been investigated in renal patients.

In patients with nephrotic range proteinuria, restriction of dietary protein intake enhances the antiproteinuric effect of ACE-I.[29] However, consideration of the individual differences in responsiveness during a normal- and low-protein diet (Figure 2) reveals that, in spite of the slightly better response during low protein intake, the individual differences in responsiveness remain strikingly large, and the poor responders by no means catch up with the good responders.

Dietary sodium restriction potentiates the antihypertensive[25] as well as the antiproteinuric[27] and renal haemodynamic[26] responses to RAAS blockade. This potentiation, consistently present in animal models and in man, occurs irrespective of the underlying disorder. Most likely, the potentiation is due to the effect of dietary sodium restriction on body volume status, as a similar effect can be obtained by co-treatment with a diuretic.[28] This potentiation is considered from an individual perspective in Figure 3, comparing the individual values of residual proteinuria during ACE-I with and without diuretic cotreatment. Again, the individual differences remain large. Despite a considerable potentiation of the responses by the diuretic, the poor responders essentially remain poor responders.

The individual response pattern to RAAS blockade, despite potentiation by sodium restriction, is well-documented, in particular in essential hypertensive patients where we first reported the individual pattern of responses of BP, renal haemodynamics and sodium excretion to ACE-I.[25,26] The between-patient differences in renal haemodynamic responses to ACE-I in these studies are illustrated in Figure 4, showing individual responses of glomerular

Figure 2 Individual antiproteinuric responses by ACE-I during a standardised normal protein diet (NPD, x-axis) versus ACE-I combined with a low-protein diet (LPD, y-axis) (Adapted from:[29]). Enhancement of the response by LPD is indicated by the regression line (continuous) shifted from the line of identity (dotted)

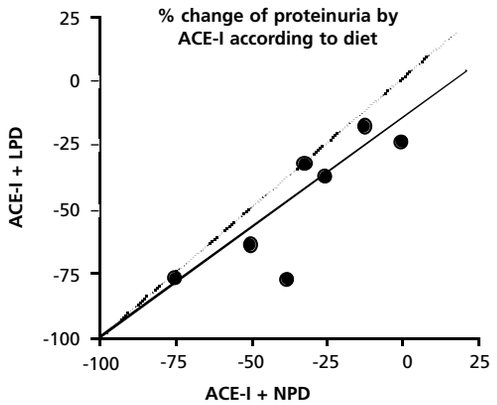


Figure 3 Individual values of residual proteinuria during ACE-I alone (x-axis) versus ACE-I combined with a diuretic (y-axis) (Adapted from:[28]). Enhancement of the response by diuretic treatment is indicated by the regression line (continuous) shifted from the line of identity (dotted)

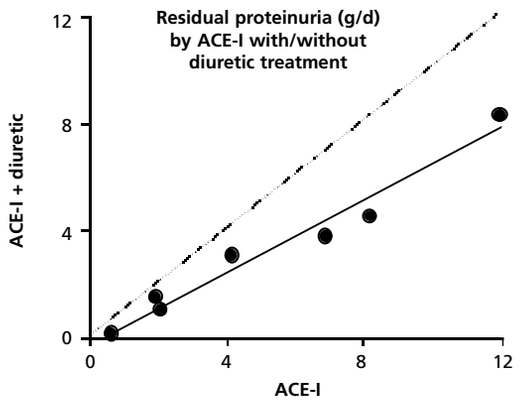
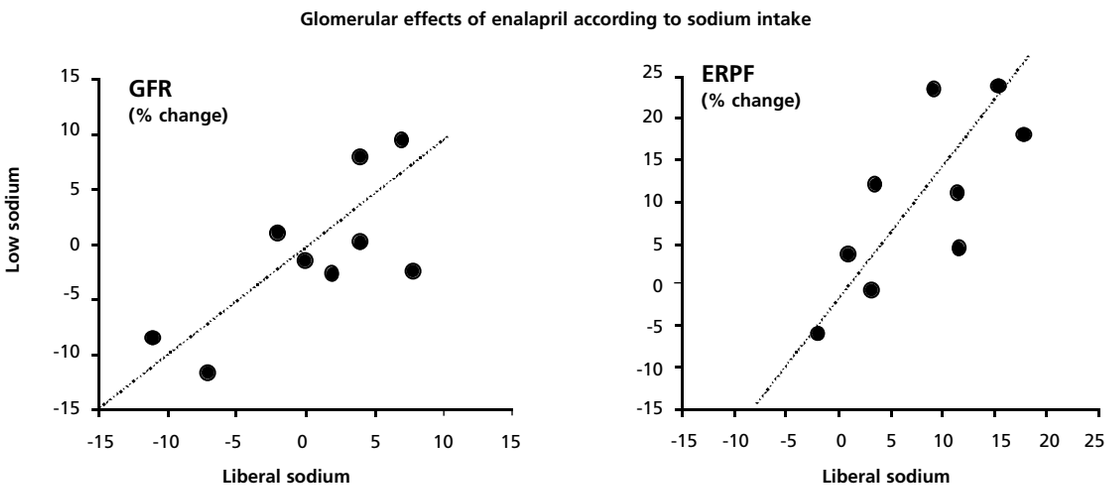


Figure 4 Effects of enalapril on glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) during liberal (x-axis, 200 mmol/d) versus low (y-axis, 50 mmol/d) sodium diet. Data are presented as the percentage change from the reference value on liberal sodium (Patient data from:[26])

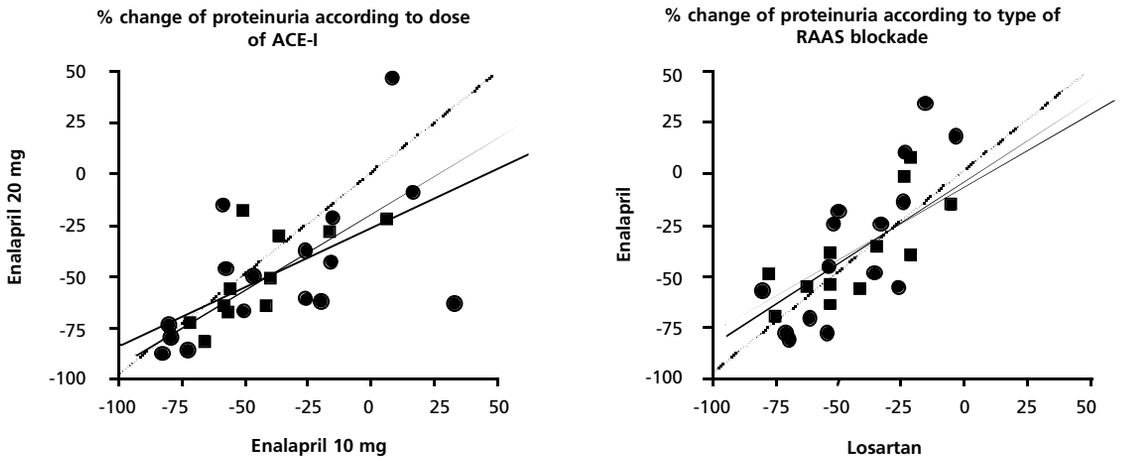


filtration rate (GFR) and effective renal plasma flow (ERPF) during liberal and low sodium intake, both depicted as the percentage change from the untreated values during liberal sodium intake. It shows, again, that the between-patient differences in renal response are considerable on either sodium intake, despite the standardised study conditions. Moreover, it is obvious that having a small or a large renal response to ACE-I is an individual characteristic that is not altered by the shift in sodium intake. Again, poor responders remain essentially poor responders. Subsequent studies with renin inhibition further substantiated the concept that responsiveness to RAAS blockade is an individual characteristic. Moreover, we were able to identify individual phenotypic characteristics that predicted individual differences in renal responsiveness to renin inhibition. The individual differences in renal response to renin inhibition were predicted by the renal haemodynamic response to sodium loading,[55] and by pre-treatment renal vascular tone,[56] respectively. Both can be considered to be a reflection of intrarenal RAAS activity; taken together, the above studies indicate that individual differences in the impact of RAAS activity on renal function determine the renal effects that can be expected from RAAS blockade.

Class and dose of RAAS blocker

Both ACE-I and ARB dose-dependently lower proteinuria and BP of diabetic and non-diabetic origin. In the Type 1 diabetic and non-diabetic renal patients, already referred to in Figure 1, we previously evaluated whether the individual response pattern might be modified by shifting to another class of RAAS blockade (i.e. from ACE-I to ARB) and by a higher dose of the drugs.[17] As a general rule, however, the individual antiproteinuric responses to both classes were strongly correlated (Figure 5, left panel) and the same was true for BP. In other words,

Figure 5 Individual antiproteinuric responses in Type 1 diabetic (circles) and non-diabetic (squares) renal patients. Left, low- versus high-dose of enalapril. Right, losartan (100 mg) versus enalapril (10 mg), i.e. doses equipotent at group level. Line of identity (dotted) is shown, as well as regression lines (continuous) for diabetics and non-diabetics separately (Adapted from:[17])



an individual was a poor or good responder, irrespective of the mode of RAAS blockade.

This is in accord with similar findings in diabetic patients, showing a close correlation between the renal haemodynamic responses to ACE-I and ARB.[40] In our study, moreover, the antiproteinuric response to ACE-I also corresponded to the response to the non-steroidal anti-inflammatory drug (NSAID) indomethacin, further supporting the notion that renal responsiveness to therapy is an individual characteristic.

Increasing the dose of the ACE-I, enalapril, from 10 to 20 mg enhanced the antiproteinuric response at a group level (Figure 5, right panel). Still, individuals with a relatively poor response to the lower dose remained poor responders at the higher dose in comparison with the other patients, and this was also observed with increasing the dose of the ARB, losartan, from 50 to 100 mg. Thus, at least within the dose range used, a higher dose improved efficacy at a group level, but could not overcome the between-patient differences in responsiveness.

Particularly in non- or poor-responding patients, it would be of interest whether further uptitration of RAAS blockade might be of benefit. In rats with proteinuria-induced renal damage, however, we found that doubling the ACE-I dose, when it was already at the top of the dose-response curve at a group level, did not improve the therapy response in non- or poor-responders[57] and the same may be true in man.[58]

It must be emphasised, however, that renoprotective treatment with RAAS blockade is traditionally titrated to reach a pre-specified target BP, rather than to reach the maximum antihypertensive effect, even although the antiproteinuric response is the strongest predictor of long-term renal prognosis. Therefore, to test whether the current practice of titrating for a pre-defined target BP results in optimal reduction of proteinuria, we analysed the effects of forced uptitration up to 150 mg daily of losartan in Type 1 diabetic and non-diabetic patients with overt proteinuria.[59] If the dose was further increased after achieving the pre-defined BP level of 125/75 mmHg, a substantial further reduction of proteinuria was still observed in many patients. Thus, specific individual titration for the antiproteinuric effect is important in order to optimise proteinuria reduction, and this may well require an increase in the dose, even if BP is well-controlled.

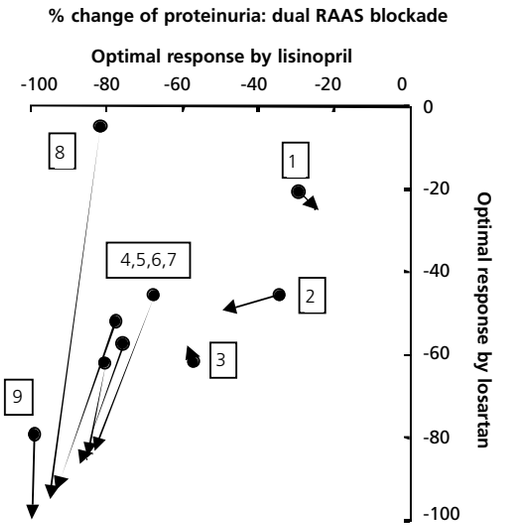
Dual RAAS blockade

Several studies have investigated the effect of dual RAAS blockade in non-diabetic,[60,61] diabetic[62] or mixed[63] renal patients and the promising results suggest that increased therapeutic efficacy may be obtained by dual as compared with single blockade of the RAAS. None of these studies, however, considered whether the doses used were at the top of the dose-response curve for the tested outcome variable (usually proteinuria). Thus, an added effect of the combination might also have been obtained by monotherapy at a higher dose.

We addressed this issue by applying dual RAAS blockade in non-diabetic renal patients after having titrated the ACE-I and ARB towards the optimal antiproteinuric dose of monotherapy for individual patients.[64] Combined treatment with ACE-I and ARB at the maximally effective individual dose was more effective than either drug alone, resulting in an average value of 85% reduction of proteinuria. These data indicate that dual RAAS blockade at optimal doses for reduction of proteinuria is effective to further reduce proteinuria at a group level.

To evaluate whether this added benefit may also help poor responders to catch up with the good responders, we analysed the individual data. Figure 6 shows the maximal antiproteinuric response of ACE-I and ARB for each patient, with the individual added effect of combined treatment indicated by arrows. As anticipated, the between-patient variability of the maximum antiproteinuric response is large, but dual blockade does not seem to make poor responders catch up with the others. In fact, the data suggest that the largest added benefit of combined treatment is obtained in patients who

Figure 6 The optimal antiproteinuric response obtained during dose-titration with lisinopril up to 40 mg/day (x-axis) and losartan up to 150 mg/day (y-axis) in individual patients. The arrows indicate the effect obtained during combined treatment with both drugs in the same patient (Patient data from:[64])



already show a good response to monotherapy (patients 4–9), whereas in patients with a poor response to monotherapy, the benefit of dual blockade seems negligible (patients 1,2). Because of its small sample size, this analysis needs further confirmation, but a recent animal study in established nephrosis yields a similar conclusion.[57] This would implicate that, in some patients, a poor response persists, despite an individual approach of dose-titration, and despite combined RAAS blockade, suggesting that different modes of intervention will be required to overcome therapy resistance in these subjects.

Future directions

In summary, between-patient differences in the therapeutic benefit of RAAS blockade are substantial. Between-patient differences in long-term renoprotection are predicted by differences in short-term renal response, which facilitates exploration of underlying mechanisms of differences in responsiveness, and evaluation of measures to overcome resistance to therapy. Several pharmacological and non-pharmacological measures improve therapeutic response at a group level, but these tools do not make the poor responders catch up with the good responders. Thus, simply prescribing a regimen with proven efficacy at a group level is not good enough, and will not cater for a substantial proportion of the patients.

In our opinion, it might be more fruitful to adopt a different treatment concept, that is guided by the response elicited in the individual patient. There is a strong rationale for reduction of proteinuria, in addition to BP control, as a titration criterion, to be adapted when side-effects such as hypotension occur. Starting from monotherapy, usually dietary sodium restriction and/or diuretic co-treatment and dose-titration will be required. If necessary, dual RAAS blockade can be applied. Although, as stated, poor responders remain poor responders in relation to others, these measures enhance therapeutic efficacy of RAAS blockade, at least to some extent, in most patients.

Patients in whom the response to therapy remains insufficient, should be a focus for future research. It is likely that, in these patients, targeting only the RAAS will be insufficient, and that the arrest of renal function decline will require a multi-drug approach,[65] combining intervention in different pathways of renal damage. To this purpose, novel therapies need to be tested against the background of RAAS blockade in selected non-responders, preferably in a stepwise approach. In the field of oncology, strategies aimed at circumvention of therapy-resistance have driven progress for a long time, and, considering the evidence for individual determinants of responsiveness in renal patients, such an approach may also give new impetus to renoprotective intervention.

Data in animal models of renal therapy resistance to RAAS blockade support the potential of such an approach. A considerable additional renoprotective effect of HMG-CoA-reductase-inhibitors (statins) was found after combined treatment, as compared with ACE-I alone.[66] Moreover, adding immunosuppression with mycophenolate mofetil to the background of RAAS blockade effectively prevented renal lesions in a severe, non-immunologically-mediated, model.[67]

We conclude that between-patient differences in responsiveness to renoprotective therapy should get specific attention as a target for intervention. Unravelling of the underlying mechanisms may allow the development of specific interventions. Based on the currently available data, we propose that response-based treatment schedules, with a multidrug approach titrated and adapted at individual responses, rather than fixed treatment schedules, may provide a fruitful strategy for more effective renoprotection.

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