High-dose angiotensin-converting enzyme inhibitor attenuates oxidative stress in patients with chronic kidney disease

Sir,

A pharmacological blockade of the renin–angiotensin–aldosterone system (RAAS) constitutes a cornerstone strategy for inhibiting progression of chronic nephropathies. In a recent NDT issue, Tomas Berl [1] discussed the improvements in renal outcome associated with maximal RAAS inhibition achieved using combined therapies that included angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), renin inhibitors and mineralocorticoid receptor antagonists. Alternatively, patients were administered ACEI or ARB at doses highly exceeding those approved for blood pressure control. Here, we elaborate on this very interesting discussion by reporting that a double RAAS blockade with high-dose ACEI attenuates oxidative stress phenomena in patients with chronic kidney disease (CKD).

In an open, randomized, cross-over study, 18 white adult patients (11 men and 7 women; mean age: 42 years) with nondiabetic proteinuric CKD were evaluated to test the hypothesis that high-dose ACEI (10 mg cilazapril) combined with standard ARB (telmisartan) therapy increases nephroprotection by lowering the level of potentially nephrotoxic, oxidative stress-dependent products. The trial treatment was based on 80-mg telmisartan therapy combined with either 5 mg cilazapril or 10 mg cilazapril for 2 months of the study; the alternative ELISA kit (Cayman Chemical Co., USA) was then used to measure the urinary excretion of 15-F2-isoprostane in the treated patients. 15-F2-isoprostane is accepted as a reliable and sensitive marker of oxidative stress in the human body [2].

It was found that the higher dose cilazapril treatment significantly reduced urinary levels of 15-F2-isoprostane relative to the control group (ANOVA P = 0.008; post hoc P = 0.044) with no changes observed in systemic blood pressure, serum creatinine or potassium levels (Table 1). This finding may be of clinical relevance, as 15-F2-isoprostane has biological activity as a potent renal vasoconstrictor [3] and has been implicated as a causative mediator in hepatorenal syndrome [4].

Interestingly enough, we have previously demonstrated that a combined therapy with telmisartan and high-dose cilazapril (doubling the dose recommended for antihypertensive treatment) has no additional effect on proteinuria [5], a finding in accordance with the observations of Berl [1]. However, our present data suggest that high-dose administration of ACEI may attenuate oxidative stress, as indicated by reduced generation of potentially nephrotoxic isoprostanes, thus providing additional renal protection for patients with CKD.

Conflict of interest statement. None declared.

Editorial Note: Dr Berl had no further comments on this letter.

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5 Tylicki L, Renke M, Rutkowski P et al. Dual blockade of the renin-angiotensin-aldosterone system with high-dose

Table 1. Serum creatinine, potassium and urinary excretion of 15-F2-isoprostane

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Randomization</th>
<th>Cilazapril 5 mg</th>
<th>Cilazapril 10 mg</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine, mean ± SEM (mg/dL)</td>
<td>1.28 ± 0.11</td>
<td>1.15 ± 0.09</td>
<td>1.20 ± 0.10</td>
<td>1.17 ± 0.09</td>
</tr>
<tr>
<td>Serum potassium, mean ± SEM (mmol/L)</td>
<td>4.49 ± 0.12</td>
<td>4.55 ± 0.11</td>
<td>4.55 ± 0.14</td>
<td>4.36 ± 0.14</td>
</tr>
<tr>
<td>Urinary 15-F2-isoprostane, geometric mean</td>
<td>0.63 (0.47–1.29)</td>
<td>0.69 (0.56–1.24)</td>
<td>0.39 (0.30–0.89)</td>
<td>0.67 (0.53–1.27)</td>
</tr>
<tr>
<td>(95% CI) (ng/mg of creatinine)</td>
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**Meningococcal vaccination and chronic kidney disease**

Sir,

We read with great interest the editorial review about vaccination and chronic kidney disease by Janus et al [1]. Although this article is focused on end-stage renal disease patients, we think that it is possible to mention the meningococcal vaccine.

This immunization is usually recommended for people exposed to a case of severe meningococcal infection, or for people travelling in endemic zones (sub-Saharan meningitis belt) in close contact with the local population. In some countries, this vaccine is incorporated in national vaccination programmes [2].

A few years ago, a risk of relapse of nephrotic syndrome was signalled, after meningococcal C conjugate vaccine [3]. However, that has been invalidated by a more recent study where no link was found between vaccination and a risk of relapse [4].

Thus the use of this vaccine, when necessary, can be recommended.

However, there is a lack of data upon the degree of the immune response to this kind of vaccine in immunosuppressed patients. For asplenic individuals, for example, a double dose of vaccine has been proposed [5].

Conflict of interest statement. None declared.

**Editorial Note:** Dr Janus et al. had no further comments on this letter.

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Letter and Reply

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**Regression of parathyroid gland swelling by treatment with cinacalcet**

Sir,

Calcimimetic compounds, such as cinacalcet, reduce parathyroid hormone (PTH) secretion in patients with secondary hyperparathyroidism, as Fukagawa et al. demonstrated in the recent NDT article [1]. However, whether calcimimetic compound can reduce the size of an already-swollen parathyroid gland (PTG) is unclear. Here we report our observations of changes in the PTG size in a single case of secondary hyperparathyroidism treated with cinacalcet.

The patient was a 59-year-old woman who had been receiving haemodialysis since December 2003 for non-diabetic end-stage renal failure. In December 2006, elevated levels of serum intact PTH and alkaline phosphatase (ALP) were found (Table 1). Ultrasound examination revealed swelling of the right upper, right lower and left upper lobes of the PTG. Intravenous administration of the vitamin D analogue maxacalcitol (Oxarol®, Chugai Pharmaceutical Co., Ltd, Tokyo, Japan) reduced the levels of both intact PTH and ALP; however, the PTG (especially the left upper lobe) gradually enlarged, and the product of the serum levels of calcium and inorganic phosphorus (Ca × Pi) reached 100 mg²/dL².

In February 2008, cinacalcet tablets (Regpara®, Kirin Pharma Co., Ltd, Tokyo, Japan) were prescribed. A low dose of cinacalcet (25 mg/day; February through April 2008) shrank the right upper and lower lobes of the PTG but did not affect the size of the left upper lobe. The dose of cinacalcet was increased in March 2008 (50 mg/day), and, as a result, the size of all PTG lobes decreased (Table 1).

The present observation suggests that (1) cinacalcet can reduce the size of PTG, and that (2) the sensitivity of the lobes of the PTG to cinacalcet can differ within a single patient. Regarding the first point, Mizobuchi et al. have reported that a high concentration of calcimimetic agent induces apoptosis in cultured hyperplastic parathyroid cells [2]. Regarding the second point, Kawata et al. have reported that the suppressive effect of cinacalcet on PTH secretion correlates negatively with the degree of calcium-sensing receptor expression in a rat model [3].

To our knowledge, this is the first report showing that cinacalcet can reduce the size of the PTG in a clinical setting. Considering the case report by Lazar and Stankus that cinacalcet can induce hungry-bone syndrome, as does parathyroidectomy [4], treatment with cinacalcet might be a curative treatment for secondary hyperparathyroidism, as is parathyroidectomy.

Conflict of interest statement. None declared.