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Letters to the Editor

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Injury, failure or success? Renin–angiotensin system inhibition in acute kidney injury

Sir,

The use of inhibitors of the renin–angiotensin system (RAS) in kidney disease requires that a balance be struck between long-term benefits to kidney health on the one hand and reductions in excretory function on the other. In proteinuric chronic kidney disease (CKD) management, some degree of functional reduction following RAS inhibition is generally considered acceptable in anticipation of longer-term preservation of kidney health. In some settings, such as pre-dialysis, it may be more important to seek maximization of excretory function and avoid RAS inhibition [1].

When it comes to acute kidney injury (AKI), RAS inhibition is perceived to be a predisposing factor. It should be noted, however, that the classification systems for AKI remain based on a reduction in excretory 'function' rather than measures of kidney 'damage'. In the case of RAS inhibition, this is more than a semantic difference. By preferentially vasodilating the efferent arteriole and removing the angiotensin II-mediated maintenance of glomerular pressure, RAS inhibition will naturally reduce excretory function in settings where intrarenal perfusion pressure is compromised. However, such a reduction in excretory function does not necessarily entail any greater injury. Lower glomerular capillary pressures have not been linked to any particular pathological lesion. Furthermore, by vasodilating the efferent arteriole, RAS inhibition may improve perfusion of the peritubular capillaries which lie downstream of the glomerular circulation. A reduction in glomerular filtration rate reduces the reabsorptive workload of the tubular cells, the common victims in ischaemic AKI. Lower excretory function consequent upon the intrarenal effects of RAS inhibition may thus be protective for tubular cells, an extension of the concept of 'acute renal success' [2]. Consistent with this, RAS inhibition was renoprotective in a number of animal models of AKI, including ischaemia [3].

Therefore, theoretically, the natural history of AKI occurring on a background of RAS inhibition thus might manifest a tendency to present greater dysfunction but more rapid/complete ultimate renal recovery relative to this initial degree of dysfunction. That said, we are of the view that discontinuation of RAS inhibition in the setting of threatened renal perfusion is mandatory to maximize excretory function, prevent incipient ATN at the pre-renal stage, and minimize the risk of a requirement for dialysis which itself carries a significant morbidity burden.

There may nevertheless be a population of patients with AKI for whom RAS inhibition is actually beneficial. When patients have already commenced dialysis for AKI and the systemic perfusion pressure is maintained/elevated, a short-term reduction in excretory function following RAS inhibition is potentially of little consequence and could be associated with longer-term benefits to renal health. Since RAS inhibitors are anti-fibrotic (via reduction of transforming growth factor-beta signalling [4]), their prompt commencement in patients with diverse kidney injuries may help prevent scarring. Tubuloprotective effects theoretically could be of benefit in glomerular pathologies compromising downstream peritubular capillary perfusion (for example vasculitis and thrombotic microangiopathies) as well as in tubular disorders (such as acute tubular necrosis).

A trial of RAS inhibition in carefully selected patients with AKI requiring dialysis would not be unethical since (i) there is a theoretical basis for benefit, (ii) animal studies have been consistent with benefit and (iii) RAS inhibitors are already advocated for the preservation of residual renal function in patients established on dialysis. Inclusion criteria for such a study would specifically need to avoid recruitment of patients at risk of systemic hypotension upon RAS inhibition. Meaningful primary end points would be recovery of independent renal function or the degree of functional recovery. Acute functional changes are a poor outcome measure for the reasons discussed. Previous observational studies have, however, used this end point in assessing the renal effect of RAS inhibition in settings such as radiocontrast administration or surgery [5]. Better evidence to tailor the appropriate use of RAS inhibition in both acute and chronic kidney disease should be of benefit to the large numbers of patients who may derive benefit, or harm, from their use.

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Unlikely association of nephrectomy post-mRCC with anti-VEGF-induced renal TMA

To the Editor:

Rini *et al.* reported that thrombotic microangiopathy (TMA), a potentially life-threatening toxicity resulting from vascular endothelial growth factor (VEGF) inhibition, may be more likely in uninephrectomized renal cell carcinoma (RCC) patients, while no patient with a non-RCC malignancy in their cohort experienced TMA [1]. Literature review as well as our personal data casts doubt on the importance of a solitary kidney in TMA resulting from VEGF inhibition [2–10] (Table 1). In 18 TMA reported cases in literature, only 6 cases of RCC patients who had experienced nephrectomy, chronic kidney disease, diabetes and hypertension have been mentioned [3,8–10]. In our personal experience (unpublished data), only 5 out of 20 TMA cases had metastatic RCC (mRCC), underwent nephrectomy and had hypertension. The other 12 literature cases [2,4–7] (66.6%) as well as our own 15 remaining TMA cases (75%) had both kidneys, and <26% of them were diabetic and/or hypertensive and/or renal insufficient (Table 1). TMA related to anti-VEGF–VEGFR agents (anti-VEGF agent such as bevacizumab or VEGF Trap, or VEGFR inhibitors such as sunitinib, sorafenib or pazopanib) is clearly a class effect, and the underlying renal and oncological conditions can, at best, be considered an undiscriminating predisposing factor. Moreover, the pathophysiology of TMA induced by the combination bevacizumab and sunitinib is clearly in relation to VEGF pathway inhibition.

Fifty percent of our patients did not show haematologic signs of TMA. Despite the fact that TMA related to anti-VEGF therapy might be selectively of renal expression, only half of the biopsied patients had grade 3 or 4 proteinuria. Therefore, TMA is under-diagnosed, and clinicians should be more attentive to mild renal anomalies in those patients. Patients showing proteinuria need special referral to nephrologists. Close follow-up of hypertension and/or proteinuria in all patients by the oncologists cannot be overemphasized.

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Table 1. Characteristics of patients who developed TMA related to anti-VEGF agents: RCC vs non-RCC malignancies

	Case reports		Our cohort	
Parameters	mRCC	Non-RCC malignancy	mRCC	Non-RCC malignancy
Median (range)	*n* = 6	*n* = 12	*n* = 5	*n* = 15
Age, years	62 (57–70)	59 (44–74)	56.5 (20–73)	70 (57–74)
Previous nephrectomy	6	0	4	0
Past medical history				
Hypertension	1	0	3	3
Diabetes	1	1	0	1
Renal insufficiency	4	1	Not available	1
Bevacizumab	3	9	3	10
VEGF Trap	0	1	0	5
Sunitinib	3	2	2	0
Proteinuria	7 (5–10.6)	3.4 (0.16–16.6)	1.96 (0.37–16.6)	1.6 (0.5–3.72)
Pu <2 g/day	0%	25%	60%	40%
SBP, mmHg	206 (157–220)	180 (160–210)	160 (110–190)	160 (155–190)
DBP, mmHg	114 (100–130)	100 (90–110)	90 (70–120)	105 (90–110)
Creatinine, mg/dL	1.7 (1.7–4.1)	2.6 (0.9–5.7)	0.98 (0.46–1.96)	0.96 (0.87–1.28)
Haemoglobin, g/L	–	–	13.5 (9.1–13.5)	10.7 (8.6–14.1)
Platelet, G/mL	–	–	85 (29–184)	170 (40–400)
Schizocytes (positive)	–	–	50%	50%
Haptoglobin, g/L	–	–	1.82 (0.1–2.69)	1.28 (0.1–3.58)
LDH, IU/mL	–	–	562 (370–950)	542 (400–2202)

TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor; RCC, renal cell carcinoma; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDH, lacticodeshydrogenase.