Reply

Sir,

We thank Drs Calo and Davis for highlighting their interesting studies. We were, in fact, aware of these studies and have used them as background in grant applications in the broader context. Our paper was not intended to be a review of the literature, since this area, we believe, is still evolving. It is always a subjective decision which references to include or not in any given publication. We felt it unnecessary to include the works cited by Drs Calo and Davis, for obvious reasons.

It should be apparent that our emphasis was on the modulatory role of transforming growth factor-β (TGF-β) on renal tissue gene expression in the setting of tacrolimus-induced nephrotoxicity, in an experimental rodent model of renal transplantation. In contrast, the studies by Calo and Davis evaluated the modulation by angiotensin converting enzyme (ACE) inhibitor treatment on Cyclosporin and tacrolimus-induced hypertension in human renal transplant models but in peripheral monocytes. In this case, the emphasis for their studies was on non-renal tissue. Due to this and the emphasis on nitric oxide in the setting of hypertension, it is clear that the focus was on the potential interaction of inflammatory cells and endothelial/vascular disease. Since we did not evaluate these issues, we could not credibly comment on them. Our studies were clearly addressing issues of immunosuppression-induced nephrotoxicity as evidenced by renal dysfunction and histological changes. These indices were not end-points of the studies by Calo et al. Calo specifically indicated in their paper that patients had normal kidney function. To illustrate this difference in focus, no published papers by Calo and colleagues could be found using various criteria of literature search on PubMED® (e.g. tacrolimus, nephrotoxicity, transforming growth factor; NADPH oxidase, tacrolimus, kidney; NADPH oxidase, tacrolimus). So, it is clear that we are talking about two different facets of calcineurin inhibitor-induced side-effects.

We would also like to reiterate the comments explained in our ‘Discussion’, that our findings of absence of gp1phox expression (i.e. phagocytic cells) together with the up-regulation of NOX-1 (i.e. a non-phagocytic NADPH oxidase) clearly distinguishes our findings from those of hypertension-induced oxidative stress. It should be noted that Calo et al. dealt solely with issues of monocyte NAPDH oxidase subunit expression in the context of hypertension. This is clearly a separate issue and we did not specifically analyze gene expression in peripheral monocyte fractions.

More significantly, the overall goals of the studies by Calo et al., vs our study, are entirely different. The focus of our published [1–5] and ongoing studies is to understand the mechanism of immunosuppression-associated nephrotoxicity in organ transplantation. Our paper published in NDT was designed to understand the direct relationship of TGF-β and oxidative stress in tacrolimus-associated nephrotoxicity in a rat renal transplantation. Our results uniquely emphasize the fact that the inhibition of TGF-β by a neutralizing antibody ameliorates nephrotoxicity but prolongs graft survival. This is completely different to the published studies of Calo et al. involving hypertension in renal transplantation. Furthermore, we are confident that Calo et al. are also aware of the fact that nephrotoxicity is the single most common limiting factor in achieving long-term graft survival in any type of organ transplantation. We wish Dr Calo and Davis had, instead, commended us on our unique and meaningful study, which we feel is a step forward in designing a newer therapeutic strategy to achieve nephrotoxicity-free immunosuppression in organ transplantation. Also, we are positive that Calo et al. will agree that the coherent ‘Discussion’, linking results and conclusions, is important for a successful publication and our intention was to cite references which were relevant to TGF-β, oxidative stress, immunosuppression and nephrotoxicity.

We sincerely hope that the concerns of Calo et al. are answered. Furthermore, we hope that their elegant published studies will find an appropriate place in our forthcoming related publications.

Conflict of interest statement. None declared.


doi:10.1093/ndt/gfm146

Advance Access publication 21 May 2007

Rapidly progressive renal failure associated with successful pharmacotherapy for obesity

Sir,

We read with interest the case report of a 55-year-old woman with rapid onset of end-stage kidney failure, following orlistat therapy to help her lose weight [1]. Since June 2004, we have been running a Weight Management Programme for obese chronic kidney disease patients, which consists of a combination of individualized dietary advice, exercise
prescription and orlistat therapy. Based on this case report, we felt it was pertinent to examine whether any patient enrolled on this programme exhibited a significant reduction in renal function. To date, we have treated 60 patients with orlistat, and 32 patients have now completed the full 12 months of the Weight Management Programme, with a resultant average weight loss of 6.6% at 6 months, with maintenance up to 12 months. Nine patients have lost enough weight to enable them to be activated on the kidney transplant list, and two of these patients have already received live-related donor kidney grafts.

We reviewed our data on eGFR in all patients who had taken orlistat for at least 6 months in the Weight Management Programme. We excluded the 23 patients who were already on dialysis prior to commencing orlistat, along with four patients who had participated in the programme for <6 months. This left us with a cohort of 33 patients with stage 3–4 chronic kidney disease (CKD), with prospectively collected data on kidney function, while taking orlistat for >6 months. Our computerized database, which receives automatic downloads of data from the laboratories every 24 h, allowed us to retrospectively examine the eGFR in the 12 months prior to their commencement of orlistat, in order to establish baseline kidney function.

As shown in Figure 1, there was no obvious change in mean eGFR in the 12 months prior to commencement of orlistat, compared to the 12 months after commencement of orlistat. In 6 of the 33 patients however, eGFR reduced by >10 ml/min in the 12 month period after orlistat was commenced. However, in most cases, the period of rapid decline was followed by one of lesser decline or recovery, and these data should be interpreted with caution in view of the fluctuating levels of eGFR both before and after orlistat. Clearly, our Weight Management Programme was not specifically designed to study the effect of orlistat on renal function, and the limitations of doing so must be acknowledged. Neither does the study control for other medications, comorbidities, cause of kidney disease nor participation in clinical trials. Nevertheless, this cohort may be the largest group of CKD patients taking orlistat whilst following a structured weight reduction programme, and despite the limitations of these data, we feel that they provide some reassurance on the use of orlistat in this patient population.

We would also like to comment on some other aspects of this report. The assumption that gastrointestinal lipase inhibition, as occurs in the presence of orlistat in the small intestine, will produce hyperoxaluria in humans, and may have accounted for the rapid deterioration in kidney function in the patient in the case report by Courtney et al. [1], warrants further discussion. Whilst we are unable to provide any direct evidence to the contrary, there are several factors which make it unlikely that orlistat itself is the causative factor.

First, the rodent study [2] referred to in the case report demonstrated an increase in urinary oxalate concentration after the addition of orlistat. Greater increases in urinary oxalate occurred with the addition of oxalate to the diet, and the presence of additional fat exacerbated this response; however, no further increase in urinary oxalate concentration was evident with the addition of orlistat in this group. Therefore, it appears reasonable to conclude that in the presence of normal levels of dietary fat (30–35%), it is the addition of dietary oxalate that significantly increases urinary oxalate concentration, rather than the addition of orlistat.

Secondly, the dose of orlistat used in the rodents was more than 14 times the equivalent dose in humans, when measured in mg/kg of body weight. This may have exacerbated the effect of the drug in the rodents and may account for the changes evident in the control group, who exhibited increased urinary oxalate and creatinine excretion over the course of the study, even though there was no increase in faecal fat with orlistat in this group. This increase in urinary oxalate without a concomitant increase in malabsorbed fat in the control group is unlikely to have been caused by the suggested mechanism of fat malabsorption increasing the formation of calcium soaps, leading to an increase in soluble uncomplexed oxalate in the gastrointestinal tract. Therefore, other contributing factors may need to be considered in all groups.

Additionally, there are existing factors in the management of CKD that largely prohibit consumption of a diet high in oxalates and provide extra calcium, which reduce the likelihood of increased absorption of oxalate and prevention of calcium oxalate crystallization in the kidney. Patients with stage 3–4 CKD generally need to ensure that serum potassium and phosphate levels are normalized via dietary means and may be encouraged to follow a diet moderately reduced in potassium and phosphate and also low in salt, to aid fluid and blood pressure management. Additionally, if required, many take calcium-based phosphate-binding medication. Foods high in oxalate are generally also high in phosphate and/or potassium, or are high in salt. Therefore, most patients with CKD stage 3–4 are already following a low-oxalate diet unintentionally, which has two implications. Firstly, they are unlikely to have a high level of available oxalate in the gut, due to reduced intake and higher availability of calcium, and secondly, there is no further dietary modification required other than what has been previously recommended to them. Thus, if these patients are also obese and treated with a lipase inhibitor such as orlistat, it is unlikely that they are at risk of intrarenal precipitation of calcium oxalate.

In our cohort of 60 patients, the use of orlistat for weight loss has been very successful when integrated into a structured, multidisciplinary weight management programme for patients with CKD. There has been no rapid ongoing decline in kidney function in any of these patients, and the existence of a relationship between increased availability of oxalates in the gastrointestinal tract and the presence of a lipase inhibitor in humans remains uncertain.

Although this case report is of interest, we do not feel that our own experience with the lipase inhibitor suggests any obvious cause for concern regarding the use of this drug in obese CKD patients, although clearly there is a need for this issue to be examined in larger scale controlled clinical trials.
Conflict of interest statement. The Weight Management Programme was established with unrestricted educational grants from Roche Products Ltd and Amgen Ltd.

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doi:10.1093/ndt/gfm203

Advance Access publication 21 May 2007

Reply—Orlistat and renal failure

Sir,

We welcome the interest of MacLaughlin and Macdougall in the use of the gastrointestinal lipase inhibitor orlistat in patients with chronic kidney disease (CKD).

We previously reported the rapid, non-recoverable decline of renal function in a patient with diabetic nephropathy, that coincided temporally with the successful use of orlistat for weight reduction [1]. There was histological evidence of extensive intratubular calcium oxalate crystal deposition.

The report by MacLaughlin and Macdougall of 33 patients with stage 3 or 4 CKD, who were treated with orlistat for >6 months as part of a weight management programme, provides some reassurance about the safety of this medication in CKD patients. Interestingly, the average weight reduction was 6.6% at 6 months, with no acceleration of CKD progression in the majority of patients. There was, however, a reduction in eGFR exceeding 10 ml/min at 6 months in 6/33 (18%). It is reasonable to suggest that the risk of hyperoxaluria will parallel the degree of weight reduction if both are due to malabsorption (our patient had an 11% weight loss after 5 months). It would be useful to determine the percentage weight loss in those patients with a more rapid decline in renal function, if there was an alternative clinical explanation for this, and the outcome of those that exhibited continued decline.

The conclusion that in the presence of a normal dietary fat intake the addition of orlistat does not make a significant difference to urinary oxalate levels in rodents is misleading. We reference directly to the results of Ferraz et al [2] ‘compared to baseline, urinary oxalate increased significantly after [standard] diet + orlistat in controls’. However, we acknowledge that the extrapolation of the results from rodent models is inherently limited for several reasons, including the dose/kg ratio and differing pathophysiology (for example, calcium oxalate urolithiasis is not a spontaneous phenomenon in rats).

The mechanism of action of gastrointestinal lipase inhibitors, the temporal association of accelerated renal function decline with the commencement of orlistat, the high degree of compliance and weight reduction, the pathological findings and the absence of an alternative plausible explanation support our proposition that intrarenal precipitation of calcium oxalate triggered the acute deterioration in kidney function in our patient [1].

The data from MacLaughlin and Macdougall support our conclusion that the majority of patients prescribed a gastrointestinal lipase inhibitor do not develop clinically significant hyperoxaluria and that additional dietary restrictions are unnecessary. Nevertheless, we would advise careful monitoring of renal function in CKD patients prescribed orlistat. The risk of accelerated loss of renal function may be particularly high in compliant patients with the most rapid weight loss.

Conflict of interest statement. None declared.

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doi:10.1093/ndt/gfm211

Letters

Advance Access publication 17 May 2007

Probencid-induced membranous nephropathy

Sir,

Nephrotic syndrome (NS) associated with probenecid therapy for gout has been previously reported [1–4]. Minimal or no abnormalities were seen on renal tissue examination. We report the first case of membranous nephropathy (MN) induced by probenecid therapy.

A 79-year-old white man was admitted for pitting oedema. His past history was remarkable for familial gout. He had been treated for the previous year with probenecid (500 mg twice daily), because of allopurinol intolerance. Serum acid uric level decreased from 10.92 mg/l to 5.88 mg/l. He denied taking any other drugs and was not exposed to industrial chemicals. One month previously, routine examination revealed blood pressure 120/70 mmHg, negative urinalysis and serum creatinine level 1.1 mg/dl, but an increase in serum uric acid to 8.4 mg/l. Probenecid daily dose was increased to 1500 mg. Two weeks later, his weight had further increased, and gross pitting oedema was noted. Urinalysis revealed a ++++ test for protein and a negative test for red blood cell. Other laboratory studies included a 24h protein excretion of 5.5g and serum albumin 2.2g/dl. Renal biopsy was done with the diagnosis of MN (Figure 1). There was no evidence of any disease (negative check-up for thoracoabdominal CT scan, cystoscopy, colonoscopy and immunological tests) or drug therapy usually associated with MN, and no other evidence of an allergic response to probenecid. Drug was discontinued and within 6 weeks, the urine was free of protein and the patient was oedema-free.