The down-regulation of NCC in rat kidney following CNI treatment was confirmed by immunohistochemical staining, and the down-regulation of KS-WNK1 was confirmed by quantitative real-time polymerase chain reaction. However, the authors did not study the phosphorylated versions of NCC. Furthermore, they conducted a toxicity investigation rather than a blood pressure study.

Most interesting is the report of acquired chimaerism in which a kidney from a patient with Gitelman syndrome (NCC deficiency) was transplanted into a non-Gitelman hypertensive recipient [5]. After transplantation, postural hypotension resulted, necessitating discontinuation of all anti-hypertensive medications used for treatment of CNI-induced hypertension. The authors basically describe an acquired Gitelman syndrome after transplantation. These prescient scholars suggested that their findings supported the potential use of thiazide diuretics in the treatment of CNI-induced hypertension, thereby supporting the work of Hoorn et al. [3].

Benefit of cyclophosphamide therapy in IgA nephritis may have been obscured by warfarin-related nephropathy in the randomized trials in which warfarin and dipyridamole were used in combination with cyclophosphamide

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Keywords: acute kidney injury; anticoagulation; warfarin

Kamei et al. [1] have recently described favorable long-term outcomes in pediatric IgA nephritis patients treated with warfarin, dipyridamole, prednisone and azathioprine. Likely, this work will revive interest in ‘combination’ therapy in the management of progressive IgA nephritis. We suggest, however, that this interest needs to be interpreted in light of a recently recognized mechanism of acute kidney injury (AKI), which we have termed warfarin-related nephropathy (WRN) [2–5]. We suggest that WRN, which is relatively common in chronic kidney disease (CKD) patients [3, 4], likely confounds the interpretation of the original randomized trials of combination therapy in adults with progressive IgA nephritis [6–8]. In these studies, the immunosuppressant was oral cyclophosphamide given in the usual doses >6 months. These studies have been interpreted as showing little or no benefit by combination therapy in progressive IgA nephritis [9]. However, since then, Ballardie has reported a randomized trial showing that, compared to the usual supportive therapy, oral cyclophosphamide at 1.5 mg/kg for 3 months followed by azathioprine therapy for 1–3 years was strongly beneficial in preventing end-stage renal disease in adults with progressive IgA nephritis [10].

Despite Ballardie’s work, there continues to be reluctance to recommend cyclophosphamide therapy for progressive IgA nephritis. The rationale is that of the three randomized trials of oral cyclophosphamide [6, 7, 10], only the Ballardie
study [10] showed clear evidence of benefit. We suggest that the apparent conflict among these studies can be resolved by taking into account the likelihood that WRN occurred in some of the patients assigned to the combination therapy of the Walker [6] and Woo studies [7], but in none of the patients assigned to cyclophosphamide therapy in the Ballardie study [10]. It is noteworthy that in the Walker study [6], which showed no evidence of benefit of combination therapy, warfarin was dosed at the higher ‘anti-coagulant’ level. In the Woo study [7], which showed some evidence of benefit of combination therapy, warfarin was dosed at the lower ‘anti-thrombotic’ level. There is clear evidence that the development of WRN requires an increase in International normalized ratio (INR) to >3.0 [2–4]. On this basis, we suggest that WRN occurred more frequently in the Walker study than the Woo study. This could account for the difference in outcome in the Walker study [6] compared to the Woo study [7].

Also, Ballardie’s protocol included prednisone. The protocols of Walker and Woo did not. This, too, could have contributed to the better outcomes in the Ballardie study compared to those of Walker and Woo.

WRN is a newly recognized syndrome in which AKI occurs when the patient is over-anti-coagulated with warfarin. Typically, the INR is ≥4.0 [2–4]. Our first description of WRN involved a renal biopsy study of nine patients who developed unexplained AKI in the setting of over-anti-coagulation with warfarin. Based on the renal biopsy findings, we concluded that the AKI was caused by glomerular hemorrhage causing extensive tubular obstruction by red blood cell casts. Each of these patients also had clinical and renal biopsy evidence of CKD. In most of these patients, serum creatinine levels failed to return to their baseline levels [2].

To explore further the association of warfarin coagulopathy with AKI, we next undertook a retrospective analysis of 103 CKD warfarin-treated patients followed in our Nephrology clinics [3]. This cohort represented all the CKD patients in our nephrology clinics who experienced an INR >3.0 while on warfarin therapy and in whom a serum creatinine was measured within 1 week of the INR >3.0 [3]. Over a 3-year period, 49 patients developed an acute increase in INR >3.0 and serum creatinine was measured within 1 week of the INR >3.0. Of these, 18 patients (37%) experienced an unexplained increase in serum creatinine ≥0.3 mg/dL (mean increase 0.61 ± 0.44 mg/dL, P < 0.0001) within 1 week of the INR >3.0. Of the 31 patients who did not experience an increase in serum creatinine of ≥0.3 mg/dL in coincidence with the INR >3.0, the mean change in serum creatinine was 0.04 ± 0.19 (P = 0.7685). We regarded the former cohort as manifesting WRN. In addition to AKI, the WRN cohort showed accelerated progression of their CKD as compared with those who did not manifest WRN in relationship to the INR >3.0.

Our most recent study of WRN involved a retrospective analysis of 15 258 warfarin-treated patients whose database is maintained in the Information Warehouse of the The Ohio State University (OSU) Medical Center [4]. During the most recent 5-year period, 4006 patients experienced an INR >3.0 and serum creatinine was measured within 1 week of an INR >3.0. Because of the large size of the data set, it was not feasible to undertake detailed individual patient assessment, as we were able to do in our assessment of the 103 CKD patients discussed above [3]. However, we did assess International Classification of Diseases-9 codes in each of the 4006 patients to assess for traditional causes of AKI, including hemorrhage. If none was found, a diagnosis of ‘presumptive WRN’ was made. We found that in the CKD cohort (N = 910), presumptive WRN occurred in 33% [4]. This is similar to the 37% incidence of WRN observed in the 103-patient Nephrology Division CKD cohort described above [3]. In the non-CKD cohort assessed from the OSU Information Warehouse (N = 3096), the incidence of presumptive WRN was 16.5%.

Presumptive WRN was significantly associated with increased age, diabetes mellitus, hypertension, cardiovascular disease, glomerular disease or the concomitant use of aspirin [4]. We suggest that the significant association of WRN with glomerular disease and aspirin therapy is relevant to the randomized trials of ‘combination therapy’ in IgA nephritis. The combination included dipyridamole, which suppresses platelet function, and might increase the risk of WRN. In addition, IgA nephritis might be especially vulnerable to WRN because hematuria is a conspicuous feature of IgA nephritis.

WRN is not usually associated with gross hematuria in humans [3, 4] nor was it seen in our recently reported rodent model of WRN [5]. So, the emergence of WRN in the combination therapy cohorts could have been easily overlooked. Consistent with the notion that WRN could have been a pervasive problem in the Walker study is that by the end of the study, microscopic hematuria was ~20% higher in the combination therapy group than in the control group (P < 0.01) [11], whereas at baseline, the degree of microscopic hematuria was not different between the study cohorts [6, 11].

In addition to the randomized trials in IgA nephritis involving cyclophosphamide and warfarin, there have been two randomized trials in IgA nephritis that involved warfarin. In the larger of the two studies, 78 children were randomized to prednisone, azathioprine, heparin–warfarin and dipyridamole or to heparin–warfarin and dipyridamole [1]. In the other study, 15 patients were randomized to warfarin monotherapy or prednisolone monotherapy [12]. In both trials, the cohort that received only the anticoagulant regimen had an outcome that was inferior to the cohort that received prednisone monotherapy [12] or prednisone and azathioprine along with the anticoagulation regimen [1].

There have also been four observational studies in IgA nephritis (the patients served as their own controls) that examined serum creatinine, proteinuria and repeat kidney biopsy (in some studies) before and after an anticoagulation regimen that included warfarin plus corticosteroids [13] or the immunosuppressant mizoribine (or azathioprine) plus prednisone [14–16]. The outcomes of these studies were that, in general, the patients improved. So, warfarin did not seem to prevent improvement. Bleeding complications were rare in these studies, likely because warfarin was dosed at the anti-thrombotic, not the full anticoagulant level, as discussed above. Thus, it is likely that WRN was not a pervasive problem in these observational trials.

There was also a meta-analysis of seven trials in IgA nephritis, in which dipyridamole or an other anti-platelet drug was compared to placebo [17]. In two of the studies, the dipyridamole was given with warfarin dosed at the
anti-thrombotic level. The meta-analysis was interpreted as showing that the anti-platelet drugs reduced proteinuria and protected kidney function. However, in general, the studies were regarded as not of high quality [17]. Further studies with rigorous design were recommended. Although these studies suggest a benefit from anti-platelet therapy, there is recent evidence that dipyridamole also is a potent inhibitor of tumor necrosis factor-α expression renal tubular fluid. This cytokine promotes fibrosis [18]. Thus, the benefits of dipyridamole could include mechanisms beyond its effects on coagulation.

In summary, taken together, these studies are not informative regarding the extent to which systemic anticoagulation by warfarin may have obscured the benefits of cyclophosphamide to treat IgA nephritis. There are a number of other clinical settings in which warfarin therapy and treatment of glomerular disease could coexist, and therefore, WRN could confound the interpretation of the efficacy of therapy aimed at the glomerular disease. For example, in patients with severe nephrotic syndrome who are being treated with an immunosuppressive therapy and then require warfarin therapy because of venous thrombotic/embolic disease or high risk of thrombotic/embolic disease or patients receiving immunosuppression therapy for active systemic lupus erythematosus glomerulonephritis and then require warfarin therapy to control an anti-phospholipid syndrome. In these settings, if the glomerular disease fails to improve, it might be the result of WRN.

In summary, we suggest that the question of whether cyclophosphamide is effective in progressive IgA nephritis should be re-visited in light of the potential confounding by WRN in the trials involving combination therapy. Until this is clarified, it seems appropriate to give cyclophosphamide the benefit of the doubt with regard to its possible efficacy in progressive IgA nephritis. After all, cyclophosphamide was effective [10] or possibly effective [7, 8] in two of the three randomized trials. Furthermore, the only trial in which cyclophosphamide failed was the only trial in which warfarin was given in full anticoagulation doses [6], which increases the risk of WRN [2–4]. Also, the Ballardie protocol of 3 months of oral cyclophosphamide followed by chronic azathioprine therapy was well tolerated and apparently efficacious [10]. We have had a similar favorable experience with this regimen in the management of lupus nephritis [19]. On this basis, we suggest that until better information becomes available, the Ballardie regimen should be considered in patients with progressive IgA nephritis who are failing steroid therapy along with conventional kidney protective therapy [20]. There is no compelling evidence to add warfarin to this regimen. Indeed, if warfarin must be used because of documented thrombotic disease, careful monitoring of INR to avoid over-anticoagulation is warranted.

Acknowledgements: The study is partially supported by a start-up fund provided by the Department of Pathology, The OSU to S.V.B.

Conflict of interest statement. None declared.

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Received for publication: 9.6.11; Accepted in revised form: 19.8.11