Case Report

Protease inhibitor therapy for HIV infection: the effect on HIV-associated nephrotic syndrome

Emma Dellow1, Robert Unwin1, Robert Miller2, Ian Williams2 and Meryl Griffiths3

1Centre for Nephrology, 2Department of Sexually Transmitted Diseases and 3Department of Histopathology, The Royal Free and University College Medical School, London, UK

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Introduction

Human immunodeficiency virus-associated nephropathy (HIVAN) was first recognized in the early 1980s as a separate clinical entity [1]. Histologically, the condition resembles focal and segmental glomerulosclerosis (FSGS); patients presenting with gross proteinuria and rapidly progressive renal failure often develop end-stage renal disease in a few weeks or months. The condition is more common in those of African origin [2] and in those whose HIV status is the result of intravenous drug abuse. Evidence suggests that the condition may be due to a direct effect of the HIV virus on the kidney.

Other renal lesions occurring in HIV-positive patients are membranous glomerulonephritis (MGN) [3] (including a form that is similar to lupus nephritis [4]), IgA nephropathy [4,5], haemolytic uraemic syndrome (HUS) [2], and immune-complex-mediated glomerulonephritis in patients with co-existent hepatitis C infection [6].

No effective treatment has been found and the majority of patients with HIVAN become dialysis-dependent. Trials of high-dose oral prednisolone have had some success in reversing the effects of both HIVAN [7] and MGN [3], as has treatment with the nucleoside analogue reverse transcriptase inhibitor (NRTI), zidovudine [8]. However, no single treatment has proven effective in reversing, or stabilizing, renal failure in HIV-positive patients.

We describe two cases of male HIV-positive patients who presented with the nephrotic syndrome and had membranous glomerulonephritis on renal biopsy (Brief preliminary clinical and pathological details of these cases have been reported elsewhere [9]). They were started on a combination regimen containing a protease inhibitor (PI) for their HIV infection and both have experienced a rapid and sustained reduction in their proteinuria, and a significant improvement in their overall renal function.

Case 1

A 32-year-old HIV-positive man presented in January 1995 with gross proteinuria of 11.97 g/l (normal range, NR < 0.06 g/l) and a plasma albumin concentration of 11 g/l (NR 35–53 g/l). Plasma urea (NR 3.0–8.0 mmol/l) and creatinine (NR 50–125 μmol/l) concentrations were 6 mmol/l and 143 μmol/l, respectively. Histology of renal biopsy tissue showed a mixed immune-complex glomerulonephritis with a predominantly membranous pattern, associated with interstitial nephritis, and which was similar to that seen in systemic lupus erythematosus (Figure 1). He was started initially on prednisolone and the angiotensin converting enzyme inhibitor (ACEI) enalapril. Gradually over the succeeding months his urine protein concentration fell to 5.95 g/l and his plasma albumin concentration rose to 23 g/l.

In March 1996 he was started on anti-retroviral therapy with two NRTIs, zidovudine and lamivudine. His pre-treatment CD4 count was 60 × 106/l and plasma HIV RNA level, 38 520 copies/ml (Roche PCR assay). By September 1996 he was still nephrotic with a plasma albumin concentration of 20 g/l. In early 1997, although his urinary protein loss had begun to fall, his plasma creatinine concentration had risen to a peak of 239 μmol/l; a repeat renal biopsy in May 1997 still showed a lupus-like membranous glomerulonephritis, but with fewer immune complex deposits. His 24-h urine protein excretion was 7 g and his plasma albumin concentration 32 g/l.

In early 1997 it was evident that he was failing to respond to his antiretroviral therapy. His plasma HIV RNA level rose to 21 900 copies/ml and his CD4 cell count fell to 100 × 106/l. His therapy was changed to a combination of the two PIs saquinavir and ritonavir, and the NRTI stavudine. His only other medication...
Fig. 1. Electron micrograph of glomerular capillary loops from renal biopsy of case 1. It shows a membranous nephropathy-like ultrastructure with a subepithelial and mesangial dense deposit, which was immunologically reactive for IgG, C3 and C1q. Original print magnification ×8000. Inset shows unusual fibrillary substructure. Original print magnification ×20000. Courtesy of Dr G V Landon.
was cotrimoxazole for prophylaxis against *Pneumocystis carinii* infection. Twelve months later, he now has only trace proteinuria on urinary dipstick testing (Multistix); his plasma albumin concentration is currently 42 g/l, and his plasma urea and creatinine concentrations are 8.7 mmol/l and 149 µmol/l, respectively. His CD4 cell count is $270 \times 10^6$/l and his HIV viral load is undetectable (<500 copies/ml to DNA).

**Case 2**

A 34-year-old man with chronic hepatitis B infection and who was diagnosed HIV-positive in 1986, presented in April 1994 with proteinuria of 4.56 g/24-h and a plasma albumin concentration of 24 g/l, having been 35 g/l the previous year. His plasma urea and creatinine concentrations were 3.4 mmol/l and 105 µmol/l, respectively. Renal biopsy tissue showed membranous glomerulopathy with patchy sparing of the glomerular basement membrane and focal interstitial nephritis. An ultrasound scan of his kidneys and bladder was normal. He was given the ACEI enalapril, which reduced his proteinuria to below the nephrotic range (1.6 g/24-h), but he remained hypoalbuminaemic (28 g/l). By June 1995 he had progressed to full blown AIDS with *cryptosporidial* diarrhoea and a CD4 count of only $60 \times 10^6$/l. He was treated briefly with zidovudine monotherapy, but he was unable to tolerate it because of nausea and anaemia.

In March 1996 he was started on the PI indinavir and the NRTI stavudine. His pre-treatment CD4 count was $20 \times 10^6$/l, his plasma albumin concentration 34 g/l and his plasma creatinine concentration 113 µmol/l. The stavudine was substituted for lamivudine in December 1996, because he developed a peripheral neuropathy. He sustained a good immunological and clinical response to this therapeutic combination. After 2 years of antiretroviral therapy he has only trace proteinuria on dipstick testing, a plasma albumin concentration of 44 g/l, a plasma creatinine concentration of $99 \mu$mol/l and a stable CD4 count of $290 \times 10^6$/l. Throughout therapy his plasma HIV RNA level has remained detectable, though low, at <10000 copies/ml.

**Discussion**

In both the cases described, substantial improvements in the degree of proteinuria and plasma albumin concentration were seen after treatment of their HIV infection with a PI-containing combination drug regimen. Therapy also resulted in a significant and sustained rise in CD4 counts and a fall in plasma HIV RNA level.

The mechanisms by which HIV induces the nephrotic syndrome and comitant renal failure in patients with such a variety of histological renal lesions are not fully understood. Laboratory and clinical evidence suggests that the virus infects glomerular endothelial and mesangial cells directly [10], and that there is an interaction between the virus and various cytokines, the most widely studied being transforming growth factor β (TGFβ). *In vitro*, high levels of TGFβ are produced by peripheral blood mononuclear cells infected by HIV, inhibiting T-cell stimulation and down-regulating the ability of CD4 cells to proliferate in response to infection [11,12].

Viral load also seems to be an important factor in determining the degree of proteinuria and renal failure. A study in 1995 by Kimmel et al. [13] found that in HIV-positive patients on haemodialysis, there was a higher incidence of measurable plasma viraemia than in HIV-positive individuals with no evidence of renal disease, or in those with chronic renal failure, but not on dialysis. There was no correlation between the severity of renal impairment and the CD4 cell count.

It is likely that the improvement in proteinuria in our two patients is a direct effect of the more potent antiviral activity of a PI-containing regimen. In case 1, although there was some improvement with dual NRTI therapy, further improvement occurred only when better suppression of plasma HIV RNA levels was achieved using a PI-based regimen. In case 2, although plasma HIV levels have remained detectable, they have remained at low levels for over 2 years.

Triple combination regimens containing a PI are now part of the standard treatment of HIV infection [14]. Unless there is an additional effect of a PI that is independent of its antiviral activity, it is likely that other combination regimens without a PI will be as effective in the treatment of HIV-associated renal disease. This, and our own observations, will need to be evaluated in future studies. We cannot necessarily extend these results to other causes of proteinuria, particularly the more widespread FSGS-like lesion, and controlled clinical trials are necessary. A note of caution must be sounded, however, because there is growing evidence that PIs have important adverse side effects, including hyperlipidaemia [15] (also a feature of the nephrotic syndrome), lipodystrophy [16–18], insulin resistance [16], nephrocalcinosis and even acute renal failure [19].

If the response to treatment of our two patients with protease inhibitors proves to be typical of HIV-induced proteinuria, this form of therapy will not only reduce the morbidity and mortality in these patients, but it will also relieve a potentially increasing burden on many dialysis units. Until now, life expectancy of HIV-positive patients receiving both haemodialysis and peritoneal dialysis has been poor when compared with non-infected dialysis patients. There is also the continuing risk of exposure of dialysis staff to infection, both through regular venepuncture on haemodialysis units and from peritoneal dialysate. If protease inhibitors can ameliorate the nephrotic syndrome and renal failure in HIV-positive patients, this will significantly improve their quality of life and life expectancy, and perhaps also the need for dialysis and its associated risks to both patients and staff.
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References


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