

Fig. 1. Vasopressor dose, serum levels of metformin and lactate during renal replacement therapy.

History and clinical presentation led to the suspicion of a metformin-associated lactic acidosis [4]. Other possible causes for lactic acidosis and circulatory failure, specifically cardiogenic or hypovolaemic shock, bowel or limb ischaemia, severe sepsis or septic shock were ruled out. The plasma level of metformin was 41.9 mg/l (therapeutic range 0.3–1.2 mg/l) and confirmed our diagnosis. Despite immediate CVVH (AV 400, with an ultrafiltration rate of 1500 ml/h and bicarbonate-based substitution solution), the patient's condition deteriorated, the norepinephrine dose had to be increased to 1.65 µg/kg/min, the serum lactate level rose (Figure 1). Since vascular access did not allow for higher ultrafiltration rates, and following the suggestion of Panzer *et al.* [5], we started an additional discontinuous haemofiltration (highflux) via a separate venous catheter. Under this combined renal replacement therapy, serum lactate decreased promptly and norepinephrine doses could be tapered off (Figure 1). Subsequently, the patient recovered completely from the acute illness.

The benefit of simultaneously combining intermittent and continuous renal replacement therapy in case of severe metformin-induced lactic acidosis with circulatory failure, as described by Panzer *et al.* [5], was confirmed in our case. Thus, the approach may be considered in other cases of this frequently fatal complication of diabetes therapy.

Conflict of interest statement. None declared.

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doi:10.1093/ndt/gfl011

Advance Access publication 27 April 2006

Remission of polyomavirus-induced graft nephropathy treated with low-dose leflunomide

Sir,

The incidence of polyomavirus (BK) induced allograft nephropathy (PVAN) has gained in clinical importance as a cause of renal graft dysfunction [1]. Treatment options are at present confined to reduction of immunosuppression with or without low-dose cidofovir [2]. Leflunomide is an immunosuppressive drug with *in vitro* and suspected *in vivo* antiviral potency and has been applied to PVAN with promising results [3].

Two living donor renal transplant recipients were diagnosed with PVAN, 117 and 70 days after transplantation, respectively [characteristics of patient 1/patient 2 respectively: age 39/51 years; renal disease: MPGN/IgA-nephritis; blood group donor/recipient: (0/0)/(A/0); CMV-serostatus donor/recipient: (+/+)/(–/–); HLA-mismatches: 3/4, cellular rejection episodes prior to PVAN: 2/1]. The diagnosis was confirmed by renal biopsy and positive quantitative BK RT-PCR (graded PVAN B/PVAN A according to [2]; 3.4 and 2.1 million copies/ml plasma, respectively). Preceding leflunomide therapy, immunosuppressive therapy was reduced and a course of immunoglobulins administered in patient 1 without effect within 3 weeks.

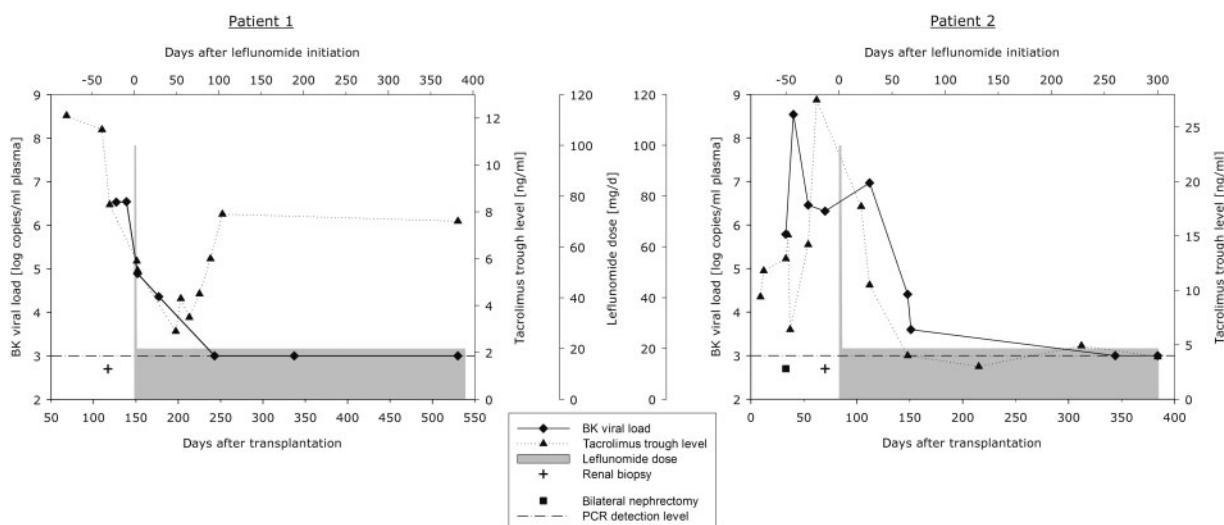


Fig. 1. Timecourse of BK viral load and therapy. Patient 1 cleared the virus 3 months after the initiation of leflunomide therapy. A preceding three week's period of lowered immunosuppression and immunoglobulins failed to improve graft function. In patient 2, higher tacrolimus drug levels prevented effective PVAN treatment with leflunomide, after adjusting the trough level to 4–6 ng/ml, the viral load decreased within 1 month and was not detectable 8.7 months after therapy. Retrospective analysis of stored plasma samples revealed high levels of viral load before PVAN diagnosis. The first peak in viral load (day 40 after transplantation) correlated to the postoperative phase of bilateral nephrectomy and subtotal adrenalectomy due to renal cell carcinoma complicated by pneumonia and postoperative adrenal gland insufficiency. Three log copies or 1000 copies per millilitre describe the PCR detection threshold.

Immunosuppression was modified by discontinuation of mycophenolate, reduction of tacrolimus (target trough level: 4–6 ng/ml) and addition of leflunomide (Arava®, Sanofi-Aventis, Frankfurt/Main, Germany, 100 mg for 3 days, 20 mg thereafter). Patient 1 cleared the virus within 3 months. At present, 13 months after therapy initiation and 17.7 months after transplantation, serum creatinine values are stable (range: 2.7–3.3 mg/dl). After leflunomide initiation, viral load in patient 2 fell rapidly. On day 261 of leflunomide therapy, the PCR became and remained negative. Graft function stabilized (range 1.6–1.9 mg/dl, 10 months after leflunomide initiation, 12.8 months after transplantation). A retrospective analysis of archived plasma samples demonstrated viral loads as high as 350 million copies/ml without overt PVAN (Figure 1).

We used a lower dose of leflunomide as in a previous report [3], which might account for the fact that no adverse reactions were observed. Lower dosing seems, nevertheless, to be effective (no graft rejection and negative PCR). Whether leflunomide exerts antiviral effects *in vivo* is still not known for certain and it may be possible that remission of PVAN is solely the effect of the reduced immunosuppression regimen. In this case, leflunomide seems at least to prevent graft rejections (none [3, this report] vs 15.3–25% [1,4]).

Important factors that need consideration seem to be close monitoring of tacrolimus trough levels (correlation of viral load with trough levels) and, in case of failing response to leflunomide, therapeutic drug monitoring of leflunomide [3].

In summary, leflunomide proved to be a safe and effective agent in the reported patients with PVAN.

Acknowledgements. The work was partially funded by a grant from Novartis, Germany.

Conflict of interest statement. The authors declare that no conflict of interest exists.

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doi:10.1093/ndt/gfl032