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BRIEF REPORT

**Didier Ducloux**
**Véronique Fournier**
**Catherine Bresson-Vautrin**
**Jean-Marc Chalopin**

# Long-term follow-up of renal transplant recipients treated with losartan for post-transplant erythrosis

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D. Ducloux (✉) · V. Fournier
C. Bresson-Vautrin · J-M. Chalopin
Department of Nephrology and
Renal Transplantation,
Hôpital Saint Jacques, Besançon, France
Fax: +33 81 21 87 81

**Abstract** Post-transplant erythrosis (PTE) develops in 9%–22% of all renal transplant recipients. Defined as a persistently elevated hematocrit (> 0.51), it occurs most commonly during the first 2 years post-transplantation in hypertensive males with excellent allograft function. Several studies have focused on a major role for angiotensin II in PTE pathogenesis, and some case reports have suggested that losartan is an effective treatment for PTE. Nevertheless, its long-term safety and efficiency have not been reported in renal transplant recipients suffering from PTE. We describe four patients successfully treated with losartan for PTE. Hematocrit remained normal for 21, 18, 15, and 15 months, respectively, after the beginning of losartan therapy. Mean erythropoietin concentration was not modified by treatment (17 ± 3.7 mU/ml vs 17 ± 3.8 mU/ml) and serum creatinine concentration remained stable. We conclude that losartan is a safe and effective long-term treatment for PTE.

**Key words** Kidney transplantation, erythrosis, losartan · Erythrosis, kidney transplantation, losartan · Losartan, erythrosis, kidney transplantation

## Introduction

Post-transplant erythrosis (PTE) is a common complication in renal transplant recipients [9, 16, 19]. Defined as a persistently elevated hematocrit (> 0.51), it occurs most commonly during the first 2 years post-transplantation in hypertensive males with excellent allografft function [15]. Following reports of anemia in renal transplant recipients undergoing ACE inhibitor (ACEi) therapy for hypertension [12, 17, 18], studies have shown that ACEi, when administered to patients with PTE, effectively reduces the hematocrit [8]. Mechanisms whereby ACEi decreases the hematocrit in patients with PTE are still unknown, even though several studies have focused on interactions between EPO production and the renin-angiotensin system [9]. Recently, specific AT1 receptor antagonists have been developed that offer the advantages of increased selectivity and specificity and that maintain a blockade of the circulatory and tissue renin-angiotensin systems at the AT1 receptor level without the adverse reactions associated with ACE inhibitors [11].

We previously reported successful treatment of PTE with losartan [4]. After this initial report, some additional cases were reported [13]. However, there is little data available about the long-term effect of losartan on PTE. We now report long-term follow-up of treatment of PTE with losartan in four renal transplant recipients.

## Case reports (Tables 1, 2)

Case 1

A 48-year-old man suffering from end-stage renal failure due to chronic glomerulonephritis received a cadaveric renal allograft in April 1995. At the time of transplantation, the recipient's hematocrit was 0.26. Induction immunosuppression consisted of polyclonal antithymocyte globulins in combination with prednisone and

**Table 1** Clinical and biological data. (*Hct* hematocrit, *SCr* serum creatinine concentration, *1* value at the beginning of losartan therapy, *2* value at the end of follow-up)

| | Age (years) | Gender | Transplant duration at the onset of PTE (months) | Losartan dosage | Hct 1 | Hct 2 | SCr 1 (μmol/l) | SCr 2 (μmol/l) | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|
| Patient 1 | 48 | M | 7 | 100 mg | 0.54 | 0.41 | 80 | 83 | 21 |
| Patient 2 | 30 | F | 16 | 100 mg | 0.52 | 0.38 | 79 | 85 | 18 |
| Patient 3 | 43 | M | 21 | 100 mg | 0.51 | 0.39 | 109 | 101 | 15 |
| Patient 4 | 39 | M | 12 | 100 mg | 0.53 | 0.37 | 117 | 113 | 15 |

**Table 2** Evolution of different parameters after successful treatment with losartan

| | Before treatment | 18 ± 3 months after treatment | *p* |
|---|---|---|---|
| S. Creatinine (μmol/l) | 96 ± 19 | 95 ± 14 | NS |
| Hematocrit | 0.52 ± 0.01 | 0.38 ± 0.02 | < 0.0005 |
| EPO concentration (mU/ml) | 17 ± 3.7 | 17 ± 3.8 | NS |

azathioprine. Immediately before completion of ATG therapy, cyclosporin was added to the immunosuppressive regimen. The immediate postoperative period was without complication. On discharge, the patient's serum creatinine concentration was 81 μmol/l. Seven months post-transplantation, serum creatinine was 80 μmol/l and hematocrit had increased to 0.54. Erythropoietin (Epo) concentration was 12.4 mU/ml (normal range 3.7–16 mU/ml) and red blood cell mass was elevated (33.1 ml/kg). Losartan (100 mg/day) was introduced because of hypertension. Within 7 weeks, the hematocrit had returned to normal (0.42) and allograft function remained stable. EPO concentration was 6 mU/ml. Twenty-one months later, he was still receiving losartan and the hematocrit was 0.41. Serum creatinine concentration was 83 μmol/l.

Case 2

A 30-year-old woman received a renal transplant in November 1994 because of end-stage renal failure due to urological malformations. Antilymphocyte globulin induction therapy was used as part of a quadruple immunosuppressive drug regimen. Long-term immunosuppression consisted of cyclosporin, azathioprine, and prednisone. The immediate postoperative period was without complication and serum creatinine concentration was 79 μmol/l on discharge. PTE developed in March 1996. Hematocrit was 0.52, Epo concentration 15.6 mU/ml, and red blood cell mass 34 ml/kg. Losartan (100 mg/day) was begun and 3 months later the hematocrit was 0.4, serum creatinine concentration 78 μmol/l, and EPO concentration 12.4 mU/ml. Eighteen months later, hematocrit was 0.38, serum creatinine concentration 85 μmol/l, and EPO concentration 13.5 mU/ml, while the patient was receiving only 100 mg/day of losartan.

Case 3

A 43-year-old man received a cadaver kidney in August 1994. Induction immunosuppression consisted of polyclonal antithymocyte globulins in combination with prednisone and azathioprine. Maintenance immunosuppression was achieved with steroids, azathioprine, and cyclosporin. The immediate postoperative period was without complication. Serum creatinine concentration was 109 μmol/l. PTE was first noted in May 1996. Losartan therapy (100 mg/day) was begun in June when the hematocrit was 0.51 and red blood cell mass 36 ml/kg. Three months later, the hematocrit was 0.41, serum creatinine concentration 111 μmol/l, and EPO concentration 19 mU/ml. Fifteen months after the beginning of losartan therapy, the hematocrit was 0.39, serum creatinine concentration 101 μmol/l, and EPO 21.5 mU/ml while the patient was still receiving losartan at 100 mg/day.

Case 4

A 39-year-old man received a cadaver kidney in June 1995. Antilymphocyte globulin induction therapy was used as part of a quadruple immunosuppressive drug regimen. Long-term immunosuppression consisted of cyclosporin, azathioprine, and prednisone. The immediate postoperative period was uneventful. Serum creatinine concentration was 117 μmol/l. Losartan therapy (100 mg/day) was begun in June 1996 when the hematocrit was 0.53 and red blood cell mass 37 ml/kg. Three months later, the hematocrit was 0.36, serum creatinine concentration 110 μmol/l, and EPO concentration 21 mU/ml. Fifteen months after the beginning of losartan therapy, the hematocrit was 0.37, serum creatinine concentration 113 μmol/l, and EPO concentration 18.7 mU/ml, while the patient was still receiving losartan at 100 mg/day.

## Discussion

PTE usually appears within the first years after transplantation. The most common symptoms are malaise, flushing, lethargy, headache, and hypertension [9]. PTE has also been linked to an increased risk for thromboembolic events [9]. Although both phlebotomies and theophylline have been used successfully in PTE, the treatment of choice is ACEi or AT1 receptor antagonists [4, 9, 13].

Mechanisms whereby ACE inhibitors and angiotensin receptor antagonists decrease the hematocrit are still unknown. Several studies have focused on a major role for angiotensin II in PTE pathogenesis. It has been shown that in rodents, hypoxia increases plasma levels of both EPO and renin. Moreover, administration of homologous renin increases plasma EPO levels, a response that is abolished by pretreatment with captopril and restored by angiotensin II infusion [10]. Angioten-

sin II increases EPO levels in anemic animals [7]. In transplant recipients, production of renin from native kidneys is increased and in those with PTE, concentrations of renin and EPO in native kidney venous blood are highly correlated [1]. Taken together, these data suggest that both ACE inhibitors and angiotensin receptor antagonists might blunt erythropoiesis by dampening angiotensin-driven EPO production in native kidneys.

Nevertheless, the absence of a decrease in EPO concentrations in most series suggests that other mechanisms are involved. Mrug et al. recently demonstrated the presence of AT1 on erythroid precursors in cultures. They also reported that activation of AT1 with AT II enhances EPO-stimulated erythroid proliferation in vitro [14]. The stimulatory effect of AT II on erythropoiesis in vitro was observed only when the erythroid progenitors were cultured with EPO. Losartan added to cultures inhibited the stimulatory effect. This result suggests that aberrant regulation in the AT1 receptor signal transduction pathway is involved in PTE patients [15].

A wide variety of factors stimulate erythropoiesis, including insulin-like growth factor, granulocyte-macrophage colony stimulating factor, IL-6, IL-1, IL-3, activin-A, and basic fibroblast growth factor [3, 18]. AT II may stimulate erythroid proliferation directly and augment the effect of either the erythropoietin signal transduction pathway or that of other erythroid growth factors.

Other mechanisms have also been implicated. ACE is involved in the hydrolysis of Ac-SKPD, a regulatory factor of hematopoesis. Ac-SKPD reversibly prevents the recruitment of pluripotent hematopoetic stem cells and normally early progenitors into the S-phase of the cellular cycle by maintaining the G0-phase [2]. It has been speculated that the action of ACEi in the treatment of PTE might be related to increased plasma levels of Ac-SKPD and a consecutive suppression of hematopoesis, but the efficiency of losartan in treating PTE argues for a direct role of angiotensin in PTE pathogenesis [5].

We recently reported the effects of losartan on hematocrit in renal transplant recipients without PTE [6]. A significant decrease in hematocrit was observed after 3 months of treatment with losartan but, as in patients with PTE, hematocrit remained stable after this initial decrease. These results suggests that neither ACEi nor losartan has a direct effect on erythropoiesis. Both ACEi and losartan reduce ATII-dependent erythropoiesis. When inhibition of AT II production or action is achieved, these therapies no longer have an effect on hematopoiesis. Withdrawal of treatment may cause a new angiotensin-driven increase in erythropoiesis and recurrence of PTE.

Many studies have demonstrated that ACEi is effective in treating PTE [12, 16]. It has been reported that discontinuation of ACEi is often followed by recurrence of PTE and that long-term treatment with ACEi is required in patients with PTE. The effect of ACEi on PTE is longlasting, and long-term administration appears to be safe in renal transplant recipients. Such data were not available concerning losartan. To our knowledge, only one case of long-term treatment of PTE with losartan has been reported [13]. Yet, the follow-up was only 11 months and losartan had to be withdrawn because of hypotension. In this study, we reported that, after a mean follow-up of $18 \pm 3$ months, losartan remained effective in treating PTE without and adverse effects. We did not observe hypotension. All of our patients had hypertension and required antihypertensive therapies. Losartan was added as a part of their antihypertensive drug regimen. Moreover, the serum creatinine concentration remained stable in patients undergoing losartan therapy ($96 \pm 19$ μmol/l vs $95 \pm 14$ μmol/l).

We conclude that losartan is safe and effective in the treatment of PTE, and we suggest that its effect on hematocrit is longlasting.

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