

Losartan, an Angiotensin II Type 1 Receptor Antagonist, Lowers Hematocrit in Posttransplant Erythrocytosis

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Abstract. The mechanism by which angiotensin-converting enzyme inhibitors reduce red cell mass in renal transplant recipients with erythrocytosis is unclear. To examine the role of angiotensin II in this disorder, losartan (a competitive antagonist of the angiotensin II type 1 [AT₁] receptor) was administered to 23 patients with erythrocytosis. Fourteen patients took 25 mg/d for 8 wk; nine others were treated with 50 mg/d for 8 wk. Hematocrit decreased from 0.527 ± 0.027 to 0.487 ± 0.045 after 8 wk ($P < 0.01$)—by at least 0.04 in 19 patients. Decrement in hematocrit in the initial 8 wk of therapy was significantly greater in patients administered 50 mg/d than in patients on 25 mg/d. Twelve of 14 patients initially treated with 25 mg/d showed a small change in hematocrit; the dose

was increased to 50 mg/d for 8 more wk. Hematocrit decreased from 0.528 ± 0.030 before losartan treatment to 0.483 ± 0.055 after 16 wk ($P < 0.01$). After therapy, serum erythropoietin significantly decreased in eight patients with elevated baseline levels, but not in 15 patients with normal baseline levels; however, hematocrit significantly decreased in both groups. Losartan was withdrawn in 16 patients; hematocrit increased from 0.440 ± 0.057 to 0.495 ± 0.049 after 8.9 ± 7.5 wk ($P < 0.001$), without change in serum erythropoietin. Thus, specific blockade of AT₁ receptors inhibited erythropoiesis, suggesting a pathogenic role for angiotensin II in posttransplant erythrocytosis. (*J Am Soc Nephrol* 9: 1104–1108, 1998)

Erythrocytosis (also known as polycythemia), an increase in red blood cell mass often defined clinically as a hematocrit greater than 0.51, occurs in 5 to 17% of renal transplant recipients within 2 yr after engraftment (1–3). Although the hematocrit may spontaneously decrease to normal on occasion (4,5), in many patients the hematocrit remains elevated for years (6,7). Because of an increased risk for thromboembolic events, many transplant programs have tried to maintain the hematocrit less than 0.55 (8). We (9) and others (10–15) have shown that angiotensin-converting enzyme (ACE) inhibitors are safe and effective therapy, often in very small doses; response usually occurs within several weeks. The basis for the efficacy of this class of agents remains unknown. To examine whether ACE inhibitors may suppress erythropoiesis by blocking a specific effect of angiotensin II, we administered losartan, a selective angiotensin II type I (AT₁) receptor antagonist recently approved for therapy of hypertension, to renal allograft recipients with posttransplant erythrocytosis (PTE).

Materials and Methods

Patients

Eighteen stable renal transplant patients on enalapril for treatment of PTE volunteered to stop the medication. To qualify for treatment with losartan, the hematocrit had to increase by at least 0.04 within the next 3 mo. Eleven patients fulfilled this criterion. An additional 12 newly diagnosed patients, with hematocrit greater than 0.51 on three consecutive clinic visits, were enrolled. No patient had clinical, laboratory, or radiographic evidence of hepatic dysfunction or pulmonary disease, or was taking an iron supplement. The doses of immunosuppressive, antihypertensive, and diuretic medications were not changed after starting losartan. Sustained-release nifedipine was used to treat hypertension in the presence of diastolic pressure greater than 105 mmHg after withdrawal of enalapril.

The study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham. Informed written consent was obtained from all patients before participation.

Treatment Protocol

At the inception of the treatment with losartan, patients were evaluated in the General Clinical Research Center. BP was measured while the patients were seated, and venous blood was drawn for baseline measurement of hematocrit, creatinine, potassium, serum erythropoietin, plasma angiotensin II, and plasma renin activity. Losartan was begun at 25 mg/d for the first 14 patients enrolled. BP, hematocrit, creatinine, and potassium were measured 4 and 8 wk later. Serum erythropoietin, plasma angiotensin II, and plasma renin activity were measured after 8 wk of treatment. Because of a decrement in hematocrit of 0.05 or less after 8 wk of treatment, the dose of losartan was increased to 50 mg/d in 12 patients (the other two patients had decrements of 0.09 and 0.10). BP, hematocrit, creatinine, and potassium were measured 4 and 8 wk later. Serum erythropoietin, angio-

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tensin II, and renin activity were measured after 8 wk of treatment with the higher dose. The last nine patients were treated with 50 mg/d from the start; BP measurements and laboratory studies were repeated on the above schedule during 8 wk of treatment.

Sixteen patients agreed to discontinue losartan after several months of treatment to assess the response to stopping treatment. Hematocrit and serum erythropoietin (in 12 patients) were measured approximately 6 wk later.

Laboratory Assays

Hematocrit was measured using a Sysmex® NE-8000 instrument purchased from Toa Medical Electronics (Kobe, Japan). Serum creatinine and potassium concentrations were measured with a SMAC-II computerized AutoAnalyzer purchased from Technicon (Tarrytown, NY). Serum erythropoietin levels were measured using an enzyme-linked immunosorbent assay kit obtained from Genzyme Corp. (Cambridge, MA). Plasma angiotensin II levels were measured by RIA purchased from Corning Nichols Institute (San Juan Capistrano, CA). Plasma renin activity was measured using modifications of methods described previously (16).

Statistical Analyses

Paired *t* tests were used to evaluate timed changes in hematocrit and serum erythropoietin, plasma angiotensin II, and plasma renin activity from baseline. The Wilcoxon rank sum test was used to compare the patient groups treated with 25 mg/d and 50 mg/d with

respect to changes in hematocrit from week 0 to week 8 of treatment. Pearson correlation coefficients were used to assess the correlation between change in hematocrit and serum erythropoietin levels. Stepwise logistic regression analyses were used to evaluate the effects of baseline values of serum erythropoietin, plasma angiotensin II, and plasma renin activity, and changes in these values from baseline on response in hematocrit, defined as a decrease of at least 0.04 after 8 wk of therapy. A *P* value less than 0.05 was considered statistically significant. Results are expressed as mean \pm SD.

Results

The 23 patients included 20 men and three women; 17 were white and six were black. Eighteen patients had received a cadaveric allograft, and five received the allograft from a living donor. All patients retained their native kidneys, and 13 were current smokers. The male predominance was consistent with the gender distribution of our total population of patients with PTE.

Treatment with losartan significantly reduced the hematocrit; the effect was apparent as early as 4 wk after starting therapy (Table 1). The decrement in hematocrit during treatment was at least 0.04 in 19 of the 23 patients; in four patients, it was 0.10 or greater. After the initial 8 wk, the decrease in hematocrit was significantly greater in the nine patients who started on 50 mg/d than in the 14 patients begun on 25 mg/d.

Table 1. Laboratory measurements in 23 renal transplant patients with posttransplant erythrocytosis treated with losartan^a

Treatment Group	<i>n</i>	Test	Week of Treatment				
			0	4	8	12	16
25 mg/d \times 8 wk	14						
		Hct	0.525 \pm 0.031	0.506 \pm 0.045	0.496 \pm 0.051		
		Epo	11.9 \pm 13.0	ND	6.4 \pm 4.9		
		A II	18.8 \pm 7.5	ND	27.2 \pm 13.0 ^b		
		PRA	1.1 \pm 0.3	ND	1.7 \pm 0.9 ^b		
25 mg/d \times 8 wk, then 50 mg/d \times 8 wk	12						
		Hct	0.528 \pm 0.030	0.517 \pm 0.035	0.510 \pm 0.038	0.492 \pm 0.049 ^b	0.483 \pm 0.055 ^c
		Epo	9.0 \pm 8.6	ND	5.7 \pm 4.4	ND	6.9 \pm 4.5
		A II	18.8 \pm 7.5	ND	27.2 \pm 13.0 ^b	ND	25.4 \pm 10.7
		PRA	1.1 \pm 0.3	ND	1.7 \pm 0.9 ^b	ND	1.5 \pm 0.5 ^b
50 mg/d \times 8 wk	9						
		Hct	0.529 \pm 0.023	0.496 \pm 0.028 ^b	0.472 \pm 0.031 ^c		
		Epo	21.6 \pm 16.0	ND	13.6 \pm 4.2		
		A II	28.6 \pm 12.7	ND	41.1 \pm 24.6		
		PRA	2.1 \pm 2.4	ND	4.3 \pm 4.7		
Total	23						
		Hct	0.527 \pm 0.027	0.502 \pm 0.039 ^c	0.487 \pm 0.045 ^{c,d}		
		Epo	15.7 \pm 14.7	ND	9.3 \pm 5.8 ^b		
		A II	23.0 \pm 11.0	ND	33.1 \pm 19.6 ^b		
		PRA	1.5 \pm 1.6	ND	2.8 \pm 3.3 ^b		

^a Values are means \pm SD. Hct, hematocrit; Epo, serum erythropoietin (mU/ml); A II, plasma angiotensin II (pg/ml); PRA, plasma renin activity (ng/ml per h); ND, not done.

^b *P* < 0.05, compared with baseline measurement at week 0.

^c *P* < 0.01, compared with baseline measurement at week 0.

^d The hematocrit decreased by \geq 0.04 in 19 patients by the end of treatment and by \geq 0.10 in four patients.

For the 12 patients with modest change in hematocrit (a decrement 0.05 or less), increasing the losartan dose from 25 to 50 mg/d for 8 more wk of treatment did not significantly decrease the hematocrit further. Among these 12 patients, two had been successfully treated previously with enalapril, but their hematocrit levels decreased by only 0.02 after 16 wk of losartan therapy, remaining above their enalapril-induced measurements.

In the 23 patients, serum erythropoietin significantly decreased after 8 wk of losartan treatment (Table 1). However, there was no significant correlation between the change in hematocrit and change in erythropoietin levels during therapy when analyzed for the total group ($r = 0.18$, $P = 0.41$) or during the 8-wk interval when 21 patients were taking 50 mg/d ($r = 0.06$, $P = 0.80$). Eight patients with baseline serum erythropoietin levels above the upper limit of normal (16 mU/ml) showed a decrease in serum erythropoietin after 8 wk of losartan treatment (28.6 ± 14.3 to 11.9 ± 4.3 mU/ml; $P = 0.02$), whereas the 15 patients with normal baseline values showed no change (7.3 ± 5.0 to 7.7 ± 6.1 mU/ml). The hematocrit significantly decreased with treatment in both groups (0.030 ± 0.032 and 0.037 ± 0.052 , respectively); these decrements did not significantly differ ($P = 0.85$). Plasma angiotensin II levels and plasma renin activity increased with losartan treatment (Table 1), but change in hematocrit did not correlate with baseline values or changes in either measurement during treatment.

Treatment with losartan was well tolerated. The baseline serum concentrations of creatinine (1.4 ± 0.4 mg/dl) and potassium (3.9 ± 0.05 mEq/L) did not significantly change in the 23 patients during treatment. No patient developed a serum potassium concentration greater than 6.0 mEq/L. The mean arterial BP for all patients decreased significantly after 8 wk of treatment with losartan (112 ± 14 to 104 ± 11 mmHg; $P = 0.02$), but no patient developed symptomatic hypotension.

Sixteen patients were withdrawn from losartan therapy; the hematocrit significantly increased from 0.440 ± 0.057 to 0.495 ± 0.049 ($P < 0.001$) after 8.9 ± 7.5 wk. Serum erythropoietin was measured in 12 patients who were off losartan for 6.0 ± 0.4 wk, during which time the hematocrit increased from 0.459 ± 0.38 to 0.495 ± 0.048 ($P = 0.008$). The serum erythropoietin level at withdrawal was 24.3 ± 17.4 mU/ml and did not significantly change (22.4 ± 12.9 mU/ml).

After completion of the study, one patient whose hematocrit had increased from 0.510 to 0.570 during 16 wk of treatment with losartan (25 mg/d for 8 wk followed by 50 mg/d for 8 wk) was switched to 10 mg/d enalapril. After 12 wk, the hematocrit progressively decreased to 0.390.

Discussion

The pathophysiologic mechanism for accelerated erythropoiesis in renal transplant recipients culminating in erythrocytosis has been debated for several years. Although various treatment regimens lower hematocrit, no unified hypothesis based on these therapies has emerged. ACE inhibitors, recently accepted as standard therapy for PTE, may suppress erythropoiesis by several mechanisms. The findings presented here

show that treatment with losartan, a specific AT₁ receptor antagonist, was safe and effective, confirming the benefit reported in case reports (17–19) and small series (20,21) in which hematocrits frequently decreased by 0.05 to 0.08, and sometimes by as much as 0.12. Our data suggest an important role for angiotensin II in the erythropoiesis in these patients.

Several investigators have postulated a central role for excess erythropoietin, produced either in the allograft or native kidneys, in stimulating erythropoiesis. Erythropoietin levels may be increased in venous blood from the retained native kidneys (22–25), and their removal lowers the hematocrit in some patients with PTE (25). Decreased erythropoietin production has also been the postulated mechanism underlying the efficacy of theophylline in treating PTE (26). Several studies have shown that angiotensin II may stimulate erythropoietin synthesis. Infusion of a subpressor dose increased erythropoietin levels in anemic animals, moreso in animals with intact kidneys than in nephrectomized animals (27). Administration of homologous renin increased plasma erythropoietin levels, a response blocked by pretreatment with an ACE inhibitor (captopril) and restored by infusion of angiotensin (28). In normal humans, intravenous infusion of angiotensin II has been shown to increase circulating erythropoietin levels (29); conversely, ACE inhibition reduced erythropoietin levels (30). In renal transplant recipients with PTE, concentrations of renin and erythropoietin in venous blood of native kidneys have been correlated (31). In some studies, erythropoietin levels were correlated with changes in hematocrit during ACE inhibitor therapy (11) or after its withdrawal (15). Taken together, these studies suggest that angiotensin II could accentuate erythropoiesis by increasing production of erythropoietin. In the present study, serum erythropoietin levels significantly decreased with losartan therapy. However, the change in hematocrit did not correlate with baseline levels or changes in levels with treatment. Furthermore, although serum erythropoietin levels decreased with losartan treatment in patients with elevated baseline levels, the decrement in hematocrit was similar to that of patients with normal baseline levels that did not change with therapy. This finding is similar to our previous experience with enalapril treatment of PTE. Patients with low serum erythropoietin levels showed a response to treatment similar to that for patients whose increased erythropoietin levels decreased with therapy (9). Thus, although a losartan-mediated decrease in circulating erythropoietin may contribute to the control of PTE in some patients, it does not appear to be the sole factor.

We postulate that the renin-angiotensin system is intimately involved in the pathogenesis of PTE. Angiotensin II may exert a local effect on erythroid precursors that may be independent of circulating levels. We recently showed that normal human erythroid progenitor cells express AT₁ receptor (32). Moreover, in the presence of erythropoietin, angiotensin II stimulated proliferation of early erythroid progenitors *in vitro*, and this effect was abolished by losartan (32). In nonerythroid tissues, binding of angiotensin II to the AT₁ receptor activates Jak-2 kinase (33), a signal transducer also required for erythropoiesis after erythropoietin binds to its receptor on erythroid progenitors. Thus, blockade of AT₁ receptors on erythroid

progenitors in the marrow could decrease erythropoiesis independently of erythropoietin in the circulation, or even locally in the marrow. Other investigators have shown that AT₁ receptor antagonists decreased the number of these receptors on the surface of cells in several tissues (34), but such an effect has not been evaluated in erythroid progenitors.

The efficacy of losartan in the treatment of PTE supports the hypothesis that ACE inhibitors suppress erythropoiesis by reducing the effect of angiotensin II. The mechanism may be a reduction of erythropoietin levels or a blockade of angiotensin II-mediated stimulation of erythropoiesis. However, we do not discount the possibility that ACE inhibitors may suppress erythropoiesis by other effects. Indeed, as was the case for two of 12 individuals in other studies (20,21), treatment of new-onset PTE with losartan was not effective in one patient who later responded to enalapril. Two patients withdrawn from enalapril showed a smaller response to losartan. A potential mechanism to account for greater responses to ACE inhibition is altered availability of acetyl-N-Ser-Asp-Lys-Pro, a tetrapeptide that decreases proliferation of early hematopoietic precursors (35). Because ACE degrades this peptide, treatment with an ACE inhibitor might increase its activity, suppressing production of red blood cells in the marrow (36). Conversely, reduced availability of the peptide may contribute to the pathogenesis of PTE, especially when circulating erythropoietin and angiotensin II levels are low, as was true for some of our patients. However, to our knowledge, this possible mechanism for the pathogenesis or response to treatment of PTE has not been examined.

We conclude that losartan effectively lowers hematocrit levels in patients with PTE. This finding, in combination with long-standing documentation of the beneficial impact of ACE inhibitors and variable changes in serum erythropoietin levels, indicates a greater pathogenic role for angiotensin II in this disorder than had been previously appreciated.

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