# Conferences and Reviews

## Erythropoietin Therapy in Patients With Chronic Renal Failure

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**Symptomatic anemia is a common complication of chronic renal failure. Treatment is now possible with the availability of recombinant human erythropoietin (epoetin alfa). Previous experimental studies have suggested that correcting the anemia of chronic renal failure may be harmful in that renal failure may be accelerated. Although experience with this drug has been primarily restricted to its use in patients with end-stage renal disease, several recent trials have been reported in patients with varying degrees of chronic renal failure. We review these studies with particular reference to the progression of renal failure and the drug's reported side effects. We conclude that the use of epoetin is beneficial and well tolerated and that there is no compelling evidence for the acceleration of renal failure associated with its use in patients.**

(Pinevich AJ, Petersen J: Erythropoietin therapy in patients with chronic renal failure. West J Med 1992 Aug; 157:154-157)

Recombinant human erythropoietin (epoetin alfa [r-HuEPO]) was approved in 1989 for use in treating the anemia of chronic renal failure. This drug is now in widespread use and has been shown to be efficacious and safe in patients with end-stage renal disease, provided that monitoring guidelines are followed.[1-3] Objective measures such as transfusion requirements,[3] exercise capacity,[4] quality of life,[4] and cognitive[5] and myocardial function[6,7] are often improved by the use of epoetin. Costs of this therapy are substantial, however, averaging about $6,000 per patient annually.[8] Patients with the anemia of chronic renal insufficiency not yet requiring dialysis constitute a subgroup that has received considerably less attention in experimental trials. We will summarize the use of epoetin in these patients and the evidence for the benefits and risks associated with its use.*

### Anemia of Chronic Renal Failure

The anemia of chronic renal failure is multifactorial. The major factor is a relative deficiency of erythropoietin synthesis by the failing kidneys.[9] Although serum erythropoietin levels are often in the "normal" range, they are inappropriately low for the degree of anemia exhibited. Other factors possibly causing the anemia, particularly in patients with end-stage renal disease, include decreased red cell survival, iron deficiency, aluminum toxicity, osteitis fibrosa cystica, folate deficiency, uremic inhibitors of marrow function, and blood loss in the extracorporeal circuit.[9] The anemia usually begins at a serum creatinine level of about 177 μmol per liter (2 mg per dl) or a glomerular filtration rate of about 0.05 liters per minute. It is characteristically normocytic and normochromic and is associated with a subnormal reticulocyte response. The severity of the anemia differs among disease types and among individual patients having the same disease. For example, patients with interstitial disease causing renal insufficiency have a greater degree of anemia than do patients with glomerular disease, whereas patients with polycystic kidney disease have a milder or no anemia.[10]

It would seem logical that epoetin therapy in a predialysis patient should not differ substantially from its use in a patient with end-stage renal disease. Details of epoetin therapeutic guidelines and side effects have been published in a number of reviews[11-14] derived mainly from data obtained from patients already on dialysis. The major problems associated with the use of epoetin in patients with end-stage renal disease include worsening of their condition or the development of hypertension, hyperkalemia, iron deficiency, and perhaps an increased incidence of thrombotic events and seizures. The frequency of these treatment-related complications in predialysis patients is under investigation, as is the question of whether predialysis epoetin therapy can accelerate the progression of kidney failure to end-stage renal disease. This last issue has been a subject of intense discussion recently in nephrology circles and will be reviewed herein along with other aspects of epoetin therapy.

### Assessing the Degree of Renal Failure

Myers and co-workers were the first to report the effect of acute changes in the hematocrit on kidney function in rats.[15] The single-nephron glomerular filtration rate (GFR) along with renal plasma flow and the other determinants of glomerular filtration were measured by micropuncture. The results are summarized in Table 1. As the hematocrit increased to polycythemic levels (0.63 [63%]), the single-nephron GFR fell significantly. This was due to a fall in the single-nephron renal plasma flow because the associated rise in the transcapillary hydraulic pressure would increase, not decrease, glomerular filtration. The creation of anemia to a hematocrit of 0.23 (23%) was associated with opposite effects—that is, an increase in single-nephron GFR and renal plasma flow and a fall in the transcapillary hydraulic pressure.

Garcia and associates, in a more relevant study, examined the effects of the long-term administration of epoetin in a

*See also "Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia" by A. J. Erslev, MD, on pages 195-196 of this issue.

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TABLE 1.—*The Effects of Acute Changes of Hematocrit in Normal Rats**

| Physiologic Variable | Rats | | | |
|---|---|---|---|---|
| | Control | Anemic | Control | Polycythemic |
| Hematocrit | 0.51 | 0.21† | 0.51 | 0.63† |
| ΔP, mm of mercury | 33 | 30† | 38 | 45† |
| Single-nephron glomerular filtration rate, nl/min | 30 | 40† | 32 | 24† |
| Single-nephron renal plasma flow, nl/min | 81 | 156† | 88 | 49† |

ΔP = transmembrane hydraulic pressure difference across the glomerular capillary

*From Myers et al.[15] †$P<.05$ versus control.

TABLE 2.—*The Effects of Epoetin in Rats With a 5/6 Nephrectomy**

| Physiologic Variable | Rats | | |
|---|---|---|---|
| | Anemic | 5/6 Nephrectomy | Epoetin Given |
| Hematocrit | 0.27 | 0.42† | 0.50‡ |
| Mean arterial pressure, mm of mercury | 123 | 143† | 166‡ |
| ΔP, mm of mercury | 34 | 48† | 58‡ |
| Single-nephron glomerular filtration rate, nl/min | 88 | 80 | 50‡ |
| Urine protein, grams/day | 0.004 | 0.015† | 0.05‡ |
| Glomerular sclerosis, % | 5.6 | 12.8† | 33.2‡ |

ΔP = transmembrane hydraulic pressure difference across the glomerular capillary

*From Garcia et al.[16] †$P<.05$ versus anemic and epoetin-treated rats. ‡$P<.05$ versus anemic and nephrectomized rats.

renal ablation model of chronic renal failure.[16] In untreated control rats, mild anemia, hypertension, progressive proteinuria, and structural renal damage developed. The results are summarized in Table 2. Relative polycythemia developed in the epoetin-treated group. Similar to the previous study, a fall in the single-nephron GFR and an increase in the transcapillary hydraulic pressure were found. Furthermore, this was associated with increased proteinuria and structural damage to the kidney. In the polycythemic group, 33.2% of glomeruli were sclerosed, compared with only 12.8% in the mildly anemic controls. Interestingly, when the controls were made more anemic, only 5.6% of the glomeruli were sclerosed. Both studies found an elevated transcapillary hydraulic pressure, which is hypothesized to be a major factor for progression in other models of chronic renal failure.[17] The authors concluded, based on their own observations and those of Myers and colleagues, that "anemia is in fact a hemodynamically favorable adaptation to chronic renal disease, and its overly vigorous correction may have adverse renal hemodynamic and structural consequences."[16(p6142)] This conclusion is consistent with previous findings that some polycythemic patients—those with cyanotic heart disease or cor pulmonale—exhibit glomerular proteinuria that is reversible with phlebotomy,[18] and in some cases structural derangements such as glomerular congestion and sclerosis develop.[19]

## Epoetin Therapy and Kidney Failure

Several studies have reported the effect of the use of epoetin in patients with progressive kidney failure (Table 3).[20-33] Most investigators used conventional epoetin dosing and monitoring guidelines with hematocrit targets in the range of 0.33 to 0.39. Administering epoetin was successful in raising the hematocrit in virtually all patients. The severity of renal impairment on entry to the study varied among the

TABLE 3.—*The Use of Recombinant Human Erythropoietin (Epoetin) in Predialysis Patients*

| Study | Patients on Epoetin Therapy, No. | Controls | Duration of Treatment | Findings |
|---|---|---|---|---|
| Brown and Friedman, 1990[20] | 8 | Self | 1 yr | No significant (NS) change in serum creatinine level |
| Hori et al, 1989[21] | 7 | Self | 4 wk | NS change in reciprocal of serum creatinine (1/cr) slope |
| Lim et al, 1989[22]; Lim et al, 1989[23] | 10 | Self | 11-29 mo | NS change in 1/cr slope and serum creatinine level |
| Onoyama et al, 1989[24] | 7 | Self | 4 wk | NS change in inulin clearance |
| Kleinman et al, 1989[25] | 7 | Placebo | 12 wk | NS change in 1/cr slope |
| Abraham et al, 1990[26] | 8 | Placebo | 37 wk | NS change in 1/cr slope and inulin clearance |
| Frencken et al, 1989[27] | 24 | Self | 8 mo | NS change in 1/cr slope |
| Eschbach et al, 1989[28] | 17 | Self | 1 yr | NS change in 1/cr slope |
| Brown and Friedman, 1989[29] | 5 | Self | 1 yr | NS change in serum creatinine level |
| Schwartz et al, 1990[30] | 8 | Self | 1 yr | Creatinine clearance decreased 0.013 to <0.005 liters/min |
| Traindl et al, 1990[31] | 19 | Self | 5-20 wk | NS change in serum creatinine level |
| Frencken et al, 1990[32] | 8 | Self | 8 wk | Inulin clearance fell from 0.0082 to 0.0074 liters/min |
| USRHEPSG, 1991[33] | 86 | Placebo | 8 wk | NS change in 1/cr slope and creatinine clearance |
| | | Self | 1 yr | NS change in 1/cr slope and creatinine clearance |
| Total | 214 | | 1-29 mo | |

USRHEPSG = US Recombinant Human Erythropoietin Predialysis Study Group

series, with the majority having baseline serum creatinine values above 265 μmol per liter (3 mg per dl). Most studies using the slope of the reciprocal of serum creatinine level versus time detected no change in the rate of progression of kidney failure before and after treatment.[34] Studies in which the decline in renal function was measured more rigorously with inulin clearances also confirmed these observations.[24,26] Furthermore, the few patients who did progress to worsened renal insufficiency or end-stage renal disease did not do so at an accelerated rate during treatment when compared with their pretreatment period. Follow-up ranged from 1 to 29 months, a time frame that is representative of the duration between the onset of severe anemia and the progression to end-stage disease.

Several explanations have been proposed for the discrepancy between the experimental findings in the two animal studies and those in patients with chronic renal failure, including that the sample size was too small, the follow-up time was too short, and insensitive means were used to monitor progression.[35,36] The most likely explanation is that these rodent models are not completely analogous to the clinical situation. In particular, Myers and co-workers studied the acute effect of an increased hematocrit to polycythemic levels, hardly a therapeutic goal in patients with chronic renal failure.[15] Moreover, Garcia and colleagues used rats with uncontrolled hypertension and a relative polycythemia in the treatment group.[16] The hypertension may have contributed independently to the progression of renal failure, and the level of hematocrit correction is much higher than that targeted in any of the patient studies. The weight of evidence thus far in humans, therefore, does not support the concerns extrapolated from these studies of animals.

Other variables besides the progression of renal failure have been evaluated in patients. Studies of the development or worsening of hypertension in predialysis patients receiving epoetin have been inconclusive, with results varying widely. In the largest study, no statistically significant change in systolic or diastolic blood pressure was noted in epoetin-treated subjects.[33] The authors did, however, note a trend toward an increased prevalence of hypertensive events in patients whose hematocrits increased at rates greater than 0.002 per day. No study has found a definitive association between predialysis epoetin use and an increased incidence of hyperkalemia, thrombosis, or seizures. Patients treated with epoetin before the development of end-stage renal disease exhibit improved quality-of-life scores similar to their counterparts who are in the end stages of disease.[25] The use of epoetin may in fact improve the quality of life to such an extent that the decision to initiate dialysis may be made more difficult as some "uremic" symptoms such as lack of energy may in fact be due to the anemia. Symptoms such as anorexia and nocturnal leg cramps, however, were shown to often persist despite the correction of anemia.[25]

## Dosage and Monitoring of Erythropoietin Therapy

Strict guidelines have been established for epoetin dosing for patients with end-stage renal disease[13]; dosage recommendations do not differ for predialysis patients. The usual starting dose is 50 to 100 units per kg of body weight per injection, administered three times a week either intravenously or subcutaneously. Predialysis patients can administer epoetin to themselves provided they have demonstrated their ability in this regard. In predialysis patients who may not need frequent medical visits, a starting dose of 100 units per kg per week can be administered on a once-per-week basis. Dosage should be reduced when the hematocrit reaches the target range of 0.30 to 0.33 or increases by more than 0.04 in any two-week period. Dose changes should generally be in the range of 25 units per kg when using a three-times-a-week schedule. If the hematocrit exceeds 0.36, epoetin therapy should be withheld until the hematocrit is 0.33 or less, and then the dose should be reduced. The median epoetin maintenance dose is about 75 units per kg three times a week but may range from 12.5 to 525 units per kg three times a week. Average maintenance dosage requirements appear to be somewhat less for subcutaneous than for intravenous administration, perhaps because the subcutaneous route provides a longer exposure of the hormone to erythroblast progenitors.[23]

Monitoring of epoetin therapy is essential.[13] Before and during therapy, transferrin saturation must be at least 0.20 (20%) and the serum ferritin level should be at least 100 μg per liter (100 ng per ml). Supplemental iron is usually required to maintain these levels. The hematocrit should be determined twice per week until it has stabilized in the target range and the maintenance dose has been established. After any dose adjustment, the hematocrit should also be determined twice a week for at least two to six weeks. It should be checked at regular intervals thereafter. Renal function and electrolyte status as well as blood pressure must also be regularly assessed. In evaluating an apparently poor response to epoetin therapy, many causes may require consideration, including iron deficiency, occult blood loss, aluminum intoxication, vitamin deficiencies, osteitis fibrosa cystica, hemolysis, or underlying infectious, inflammatory, malignant, or hematologic processes.

## Conclusion

The anemia of chronic renal failure in predialysis patients can be successfully corrected with epoetin therapy using management guidelines developed for patients with end-stage renal disease. Its use in predialysis patients may be associated with similar side effects. The quality of life is improved as anemia is corrected in patients before the progression to end-stage disease, similar to that in patients with irreversible renal failure. An important note is that correcting anemia does not appear to accelerate the progression of renal insufficiency in humans. We recommend that anemic predialysis patients be cautiously prescribed epoetin therapy, provided that therapeutic and monitoring guidelines are followed.

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