

## Erythropoietin

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### GUIDELINES

**The weight of clinical evidence indicates that erythropoietin exerts neither a beneficial nor deleterious effect on the progression of renal impairment in patients with chronic renal insufficiency. (Level II Evidence, 6 small randomised controlled trials; clinically relevant outcomes; inconsistent effects)**

### Background

Erythropoietin is routinely used to correct the anaemia associated with chronic kidney disease (CKD). Early experience with this drug (in relatively high doses) in clinical and experimental chronic kidney failure (CKF) suggested that erythropoietin may have been deleterious to renal function, although this effect was not apparent when blood pressure was adequately controlled (Reudin et al 1991). More recent experiences with lower dosages of erythropoietin have not reported adverse effects on renal function. The objective of this guideline was to review the available clinical evidence pertaining to the effect of erythropoietin on renal failure progression.

### Search strategy

**Databases Searched:** Medline (1999 to November Week 2 2003). MeSH terms for kidney disease were combined with MeSH terms and text words for erythropoietin therapy. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and MeSH terms and text words for identifying meta-analyses and systematic reviews. The Cochrane Renal Group Specialised Register of Randomised Controlled Trials was also searched for relevant trials not indexed by Medline.

**Date of Search:** 16 December 2003.

### What is the evidence?

There are 6 randomised controlled trials.

Roth et al (1994) conducted a 48-week, prospective, randomised, open-label, multi-centre trial in which 83 anaemic predialysis patients (plasma creatinine 3–8 mg/dl) were randomly assigned to no treatment (n = 43) or treatment with erythropoietin (50 IU/kg subcutaneously three times weekly, n = 43). Allocation concealment was not specified.

The dose of erythropoietin was titrated to maintain a haematocrit level of 35%. GFR was evaluated by <sup>125</sup>I-iothalamate clearance at weeks 1, 8, 16, 32 and 48 weeks. The two groups were similar at baseline. The overall decline in GFR was identical for the two groups (−0.43 mL/min/month). The major limitation of the study was the very high drop-out rate (42%).

A prospective, single centre, randomised, open-label controlled trial (Kuriyama et al 1997) was conducted in 108 Japanese patients over 36 weeks. Anaemic CKD patients with a plasma creatinine concentration between 2 and 4 mg/dL (mean 2.9) and a haematocrit < 30% were randomly assigned to treatment with (n = 42) or without (n = 31) erythropoietin. Untreated non-anaemic (haematocrit > 30%) CKD patients (n = 35) were also recruited. Just over half the patients were diabetic and 60%–68% of patients in each group were receiving ACE inhibitors. All patients were treated with a 0.6 g/kg/day protein diet. Erythropoietin doses were adjusted to maintain haematocrit between 33% and 35% in the treated group. Mean haematocrit increased significantly in the treated group (27.0%–32.1%), but declined significantly in the other two groups. Cumulative renal survival, derived from the time it took baseline plasma creatinine concentration to double, was significantly better in the treated group than in the untreated anaemic group, but was not different from that in untreated non-anaemic controls. Dialysis was commenced in 33%, 65% and 37% of patients, respectively (p < 0.05). The improvement in cumulative renal survival in the erythropoietin-treated group was attributable solely to improved renal survival in non-diabetics. It was concluded that reversal of anaemia by erythropoietin retards the progression of renal failure, especially in non-diabetic patients (they speculated that this was due to prevention of renal tissue hypoxia). However, significant limitations of the study were (a) the use of plasma creatinine as a marker of renal function; (b) the high drop-out rate (17%); (c) the potential for sample bias in view of differences in baseline characteristics of the groups (creatinine clearances tended to be lower and 24-h urinary protein excretion rates tended to be higher in the untreated anaemic patients); and, (d) lack of adjustment for these potential confounders in the survival curves (eg by a Cox's proportional hazards model). It is also questionable that allocation concealment was adequate.

A prospective, multicentre, randomised, open-label controlled trial evaluated the effects of haemoglobin normalisation (135–160 g/L) vs maintenance of subnormal haemoglobin levels (90–120 g/L), with or without erythropoietin therapy, in 416 Scandinavian patients with renal anaemia treated across 62 hospital centres in Sweden, Norway, Finland and Iceland (Furuland et al 2003). Of the 416 study subjects, 46 patients were predialysis and had their renal function measured at baseline and at two years by local routine methods (creatinine clearance, iothalamate clearance or Cr-EDTA clearance). GFR decline was comparable between the two groups (p = 0.43). The major limitation of the study was its small sample size and lack of statistical power.

In a two-year, prospective, multicentre, randomised, open-label controlled trial conducted in Australia and New Zealand, Roger et al (2004) randomly allocated 155 patients with CKD (creatinine clearance 15–50 mL/min) to receive erythropoietin as necessary to maintain haemoglobin concentration between 120 and 130 g/L (group A) or between 90 and 100 g/L (group B). This trial was sponsored by Janssen-Cilag. By the end of two years of follow-up, the mean achieved haemoglobin concentrations were 121 ± 14 g/L for Group A and 108 ± 13 g/L for Group B. The decline in renal function

over two years, as determined by isotopic measurements of GFR, did not differ significantly between the two groups ( $8 \pm 9$  versus  $6 \pm 8$  mL/min/1.73 m<sup>2</sup>). Significant limitations of the study included (a) lack of statistical power due to small size and a failure to reach haemoglobin target for many patients in Group B; and (b) a much higher drop-out rate in Group B (25%), compared with Group A (12%), raising the possibility of survivor bias and informative censoring.

Using plasma creatinine, reciprocal plasma creatinine or creatinine clearance to assess progression of renal insufficiency, other prospective studies (Lim et al 1990, Eschback et al 1989, Lim et al 1989, Frenken et al 1989, Abraham et al 1990, Koch et al 1995, Watson et al 1990, Lim 1991, Onoyama et al 1989, Mitwalli et al 1993, Branger et al 1995) including an additional three randomised, double-blind, placebo-controlled trials (Lim et al 1989, Kleinman et al 1989), have not observed any significant effect of erythropoietin on renal function. The use of plasma creatinine or creatinine clearance as an index of renal function is a major limitation of all of these studies, particularly since erythropoietin may have significant effects on appetite (Roth et al 1994) and muscle metabolism (Park et al 1993).

A recent retrospective cohort study has also suggested that erythropoietin treatment may slow the progression of renal failure (Jungers et al 2001). In this study, the authors compared 20 patients with CKD who were treated with erythropoietin with 43 patients who had a similar degree of renal failure but who were less anemic and thus did not receive erythropoietin. The rate of decline of creatinine clearance did not change over time in the control group, whereas in the treated group, it was significantly slower after epoetin treatment had been started ( $-0.36 \pm 0.16$  mL/min per 1.73 m<sup>2</sup> per month versus  $-0.26 \pm 0.15$  mL/min per 1.73 m<sup>2</sup> per month;  $P < 0.05$ ). The significant limitations of this trial were (a) retrospective design (potential for recall bias); (b) selection bias (erythropoietin-treated patients were older, had a higher proportion of females, were less likely to be diabetic and possibly had a longer duration of uraemia); (c) lack of statistical adjustment for differences in characteristics between the two groups; and, (d) the use of creatinine clearance as an index of renal function.

## **Summary of the evidence**

Of the 6 RCTs published to date, 5 trials have found no significant effect of erythropoietin administration on the progression of CKD. One trial with significant flaws observed that erythropoietin significantly retarded renal failure progression, primarily in non-diabetics.

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**International Guidelines:** No recommendation.

### **Implementation and audit**

No recommendation

### **Suggestions for future research**

A meta-analysis of the 6 RCTs performed to date is recommended.

Out of date

## **References**

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## Appendices

**Table 1 – Characteristics of included studies**

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Roger et al, 2003	155	Randomised prospective open-label controlled trial	Multicentre trial conducted in Australia and New Zealand	155 adult patients with chronic kidney disease	Epoetin $\alpha$ as necessary to maintain Hb between 120 and 130 g/L	Epoetin $\alpha$ was initiated if Hb was < 90 g/L at clinical visits 2 months apart or was < 80 g/L at any visit.	24	
Furuland et al, 2003	416	Randomised prospective open-label controlled trial	62 hospital centres in Sweden, Norway, Finland and Iceland	416 Scandinavian patients with renal anaemia (pre-dialysis, HD or PD)	Normal haemoglobin group: epoetin alfa to achieve target Hb levels of 135–150 g/l in females and 145–160 g/l in males.	Subnormal haemoglobin group: target haemoglobin level of 90–120 g/l with or without epoetin $\alpha$ treatment	11.5–17.5	
Kuriyama et al, 1997	108	Randomised prospective open-label controlled trial	Single centre	108 anaemic Japanese patients with chronic renal failure	6000 IU of IV EPO once/week for 36 weeks	No EPO therapy	18–36	

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Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Kleinman et al, 1989	14	Randomised double-blind controlled trial	Single centre	14 non-dialysed patients with chronic renal failure and severe anaemia	100 U/kg r-HuEPO 3 times/week for 12 weeks or until 38% to 40% haemocrit target attained	Placebo	3	
Lim et al, 1989	14	Four-arm randomised double-blind controlled trial	Single centre	14 adult patients with renal insufficiency and anaemia	50, 100 or 150 U/kg r-HuEPO (IV) 3 times/week	Placebo	2	
Roth et al, 1994	83	Randomised parallel-group, open-label controlled trial	11 study centres in the USA	83 adult pre-dialysis patients with anaemia	50 U/kg r-HuEPO 3 times/week	No EPO treatment	11	

**Table 2 – Quality of randomised trials**

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis †	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Roger et al, 2004	Computer-generated	No	No	Yes	Yes	0
Furuland et al, 2003	Not specified	No	No	No	Unclear	Unclear
Kuriyama et al, 1997	Not specified	No	No	No	Unclear	Unclear
Kleinman et al, 1989	Not specified	Yes	Yes	No	Yes	0
Lim et al, 1989	Third party (pharmaceutical company)	Yes	Yes	No	Yes	0
Roth et al, 1994	Not specified	No	No	No	Unclear	Unclear