SITUATIONS HORS-AMM POUR LESQUELLES L'INSUFFISANCE DES DONNÉES NE PERMET PAS D'ÉVALUER LE RAPPORT BÉNÉFICE/RISQUE

Erythropoïétines

Bêta-thalassémie
Drépanocytose
Anémie post- transplantation d'organes solides
Anémie lors d'une CEC ou au décours d'une chirurgie cardiaque
Anémie du post-partum
Anémie des patients HIV
Anémie des patients en insuffisance cardiaque chronique

- **Bêta-thalassémie**

Les thalassémies constituent un ensemble hétérogène de maladies génétiques dues à des anomalies des gènes de l'hémoglobine.

Il existe 3 tableaux cliniques de β-thalassémie :

- la β-thalassémie mineure, qui correspond à la forme hétérozygote le plus souvent asymptomatique sur le plan clinique ;
- la β- thalassémie majeure, qui requiert des transfusions régulières ;
- la β-thalassémie intermédiaire avec des besoins transfusionnels occasionnels ou absents.

Certaines thalassémies intermédiaires ont un taux d'hémoglobine bas de façon prolongée retentissant sur la qualité de vie et bénéficient de ce fait de transfusions régulières.

Les études publiées entre 1992 et 2006 montrent un effet bénéfique de l'EPO chez les patients atteints de β-thalassémies intermédiaires ou dépendantes des transfusions. Il s'agit de petites séries ouvertes non randomisées de patients traités le plus souvent de moins de 3 mois, par EPO à la dose de 500 unités/kg 3 fois/semaine.

Deux études menées sur un faible effectif de patients ayant une bêta-thalassémie intermédiaire ou majeure (Bourantas 1997 et Rachmilewitz 1995) montrent une augmentation de 2.0 à 2.7 g/dl de la concentration d'hémoglobine. Les transfusions ont pu être arrêtées chez quelques patients. La tolérance a été bonne, aucune thrombose n'a été observée.

En 2004, une série française de 5 patients adultes β-thalassémiques splénectomisés dépendant des transfusions, la prescription d'EPO à une dose comprise entre 30 000 à 60 000 U/semaine (dose de 1 000U/kg/semaine) a entraîné une diminution des besoins transfusionnels avec un bénéfice sur la surcharge en fer, effet soutenu sur le long terme (plus de 4 ans pour 4 patients sur 5). Deux patients ont pu être sevrés des transfusions. Un des patients a présenté une thrombose porte 4 ans après le début du traitement, qui a donc été arrêté.

L'association de l'EPO avec l'hydroxyurée s'accompagne d'une amélioration clinique avec une augmentation de la concentration d'HbF dans l'étude ouverte d'El Hazmi (1995).

L'utilisation des EPO dans la bêta-thalassémie ne concerne qu'une quarantaine de patients/an en France et doit être justifiée au cas par cas après avis d'un centre de référence (Pr Galacteros - hôpital Henri Mondor - Créteil, Dr Thuret - hôpital de la Timone - Marseille.)

Il existe un registre français des bêta-thalassémies.

Traitement des anémies des sujets bêta-thalassémiques par l'EPO alfa

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Singer (2005)	**Ouverte** **N = 62** Thalassémie E/β^0	- Hu 18-20 mg/kg pdt 24+- 9 mois : n = 45 : - Hu + phénylbutyrate de sodium pdt 6 mois : n = 8 - Hu + EPO pdt 6 mois suivi par 3 ans d'observation : n = 9	> 3 ans	[Hb F] [Hb] Effet de l'Hu	-Effet de l'Hu : [Hb] ↑ de 1.3 g/dL chez 40% des patients [Hb F] : ↑ **S** (**p< 0.001**) 27/47 ont arrêté les transfusions 13/27 sont restés indépendants des transfusions lors du suivi 6/13 ont continué un traitement par Hu. L'addition de phénylbutyrate n'a pas d'effet
Nisli (1997)	**Ouverte** **N= 26** - β-thalassémie majeure	rHuEPO 500 UI/kg sc 3/sem. pdt 2 mois Si [Hb] < 8 g/dL dose x 2 pdt 4	12 M	- [Hb] > 8 g /dL - Nbre de CGR - [Hb F] - Cellules F	- A M2 : [Hb] < 7 g/dL : n = 20 patients arrêtent l'étude - A M6 : [Hb] < 7 g/dL : n = 3/6 arrêtent l'étude

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
		sem. - Fer PO : n = 16 - Pas de transfusion			- A M12 : n = 3
Bencaiova (2006)	**Ouverte** **N = 19** Femmes enceintes (en moyenne 28 sem de grossesse) ayant des hémoglobinopathies hétérozygotes (essentiellement β-thalassémiques)	Phase initiale : EPO : 3x10 000UI + Fer IV Pour les non-répondeurs : EPO : 20 000 UI	4 sem	[Hb]	↑ [Hb] et ↑ érythropoïèse : 19/19 - Bonne réponse : 13/19 : ↑ [Hb] de 1.6 g/dL - Résistance au traitement : 6/19
Nisli (1996)	**Ouverte** **N= 10** - β-thalassémie intermédiaire	500 à 1000 UI/kg sc 3 /sem. pdt 3 m	3 M	- ↑ [Hb] ≥ 2g/dL - Nbre de CGR	A M2 : n = 8 - [Hb] : ↑ de 2 g/dL à 8.03 et 10.3 g/dL - [Ht]. : ↑ de 26.6 à 33.8% - Nbre de réticulocytes : ↑ de 151x10^9 à 412 x 10^9 /L 0 CGR - Amélioration de la qualité de vie : 5/10 - Après arrêt du traitement, valeurs des paramètres évalués reviennent aux valeurs de départ - Bonne tolérance
Chaidos (2004)	**Ouverte** **N= 10** - β-thalassémie intermédiaire (5) et majeure (5) - 7/10 dépendants des transfusions	150 UI/kg sc 3 x /sem. Transfusions	12 sem. à 2 ans	- [Hb] et [HbF] - Nbre de CGR	- patients transfusés : n = 5/ 7: Nbre de CGR : ↓ **S** de 30.54 à 24.56 (**p=0.028**) [Hb] ↑ **NS** de 9.2 à 9.7 g/dL [HbF] ↑ **NS** de de 56.4 à 62.8% - Patients non transfusés : n = 3 [Hb] ↑ - 2 /7patients transfusés arrêtent l'étude car [Hb] n'↑ pas
Cozma (1995)	**Ouverte** **N=10** β-thalassémie intermédiaire 3 /10 splénectomisés	rHuEPO 500 UI/kg x3/sem pdt 12 sem puis 1000 UI/kg x3 si NR	24 sem.	- [Hb] (↑ ≥ 2 g/dL) - [HbF] - Cellules F	- [Hb] : ↑ : n = 8/10 - [Hb] et [HbF] : **≠ NS**
Rachmilewitz (1995)	**Ouverte** **N=10** β-thalassémie 6/10 patients splénectomisés	EPO sc X 3/ sem de 500 à 950 UI/kg de 5 à 12 sem. Fer : 305 mg/j Ac folique : 5 mg/j		- [Hb] - GR - Cellules F - [HbF] - [Fe]	- Splénectomisés : n = 6 . [Hb] : ↑de 7.1 à 9.3 g/dL . GR : ↑ de 4 à 5.10^{12} /L - arrêt des transfusions : n = 2 - Cellules F : . ↑ de 31 à 93% : 3/6 splénectomisés **(p < 0.003)** - Non-splénectomisés : n = 4 . Cellules F : ↑ de 56 à 80% : n = 1/ 5 . [HbF] : **NS** : n =3.
Bourantas (1997)	**Ouverte** **N= 4** - β-thalassémie	- rHuEPO : 500 UI/kg sc 3x /sem. - Sulfate de fer PO : 300 mg/j - Ac folique : 5 mg/j	6 M à 1 an	- [Hb] et [HbF] - Nbre de CGR	. [Hb] :↑ **S** de 2.5 g/dL . [Ht] : ↑ **S** de 5-7% (**p<0.005**) . [HbF] : ↑ **NS** de 53.7 à 55.2 g/dL - Nbre de CGR en péri et postop : ↓ de 83% - Nbre de jours d'hosp. : ↓ de 1.5 j - Nbre de GB et de la LDH : **≠ NS**

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
					- Bonne tolerance
Olivieri (1992)	**Cas rapportés :** **N=3** β-thalassémie intermédiaire	Dose ↑ de 300 à 1000 UI/kg x 3/sem. en sc	18 sem.	[Hb] et [HbF]	- [Hb] :↑de 7.4 à 10.5 g/dL : n =2/3 patients - [HbF] : **≠ NS**
Rachmilewitz (1998)	- Revue : Patients β-thalassémiques intermédiaires	rHuEPO : 500 à 1 000 UI/kg 3x/sem Dose minimale : 500 UI/kg - Hu seule : 20 mg/kg 4x/sem Ou rHuEPO : 500 UI/kg x3/sem ou 375 UI/kg x2/sem ou rHuEPO + Hu	9 mois 3-6 mois	Erythropoïèse [HbF] VCM CMH [Hb]	↑ érythropoïèse sans modifier les % d'HbF, MCV, MCH surtout chez les patients splénectomisés Pas d'effets indésirables sur une période de 9 mois de traitement continu Effet positif de l'association Hu + EPO sur [HbF] et RBC et sur la qualité de vie mais [Hb] **≠ NS**

GR : globules rouges
GB : globules blancs
[Hb] : concentrationd'hémoglobne
NR : non-répondeur
LDH : lactate déshydrogénase
CGR : concentré de globules rouges
[HbF] : concentration d'hémoglobine fœtale
VCM : volume moyen de la cellule
CMH : teneur moyenne en Hb
Hu : hydroxyurée

Bibliographie

Les référentiels de la Juste prescription du CEDIT (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 1992.

1. Singer ST, Kuypers FA, Olivieri NF, Weatherall DJ, Mignacca R, Coates TD, Davies S, Sweeters N, Vichinsky EP; E/beta Thalassaemia Study Group. Fetal haemoglobin augmentation in E/beta(0) thalassaemia: clinical and haematological outcome. Br J Haematol. 2005 Nov;131(3):378-88.
2. Bencaiova G, Krafft A, Burkhardt T, Breymann C. . Variable efficacy of recombinant human erythropoietin in anemic pregnant women with different forms of heterozygous hemoglobinopathy . Acta Haematol. 2006;116(4):259-65.
3. Nisli G, Kavakli K, Aydinok Y, Oztop S, Cetingül N, Basak N. Recombinant erythropoietin trial in children with transfusion-dependent homozygous beta-thalassemia. Acta Haematol. 1997;98(4):199-203.
4. Chaidos A, Makis A, Hatzimichael E, Tsiara S, Gouva M, Tzouvara E, Bourantas KL. Treatment of beta-thalassemia patients with recombinant human erythropoietin: effect on transfusion requirements and soluble adhesion molecules. Acta Haematol. 2004;111(4):189-95.
5. Cozma G. Beneficial use of EPO in sickle cell disease and Thalassaemia intermedia : interim results. Sickle cell disease and Thalassaemia: new trend in therapy. Eds Y Beuzard, B Lubin, J Rosa.1995, vol.234 p207
6. Rachmilewitz EA. Sustained increase in Hb and RBC following long term administration of EPO to patient with homozygous beta-thalassaemia. Brit J Haema. 1995, 90: 341-5
7. Bourantas K, Economou G, Georgiou J. Administration of high doses of recombinant human erythropoietin to patients with beta-thalassemia intermedia: a preliminary trial. Eur J Haematol 1997 Jul;59(1):65.
8. Olivieri NF, Freedman MH, Perrine SP, Dover GJ, Sheridan B, Essentine DL, Nagel RL. Trial of recombinant human erythropoietin: three patients with thalassemia intermedia. Blood. 1992 Dec 15;80(12):3258-60
9. Nişli G, Kavakli K, Vergin C, Oztop S, Cetingül N. Recombinant human erythropoietin trial in thalassemia intermedia. J Trop Pediatr. 1996 Dec;42(6):330-4.
10. Rachmilewitz EA, Aker M. The role of recombinant human erythropoietin in the treatment of thalassemia.
Ann N Y Acad Sci. 1998 Jun 30;850:129-38.
11. Makis AC, Chaliasos N, Hatzimichael EC, Bourantas KL. Recombinant human erythropoietin therapy in a transfusion-dependent beta-thalassemia major patient. Ann Hematol. 2001 Aug;80(8):492-5.
12. Perrine SP, Castaneda SA, Boosalis MS, White GL, Jones BM, Bohacek R. Induction of fetal globin in beta-thalassemia: Cellular obstacles and molecular progress.Ann N Y Acad Sci. 2005;1054:257-65.
13. Quek L, Thein SL. Molecular therapies in beta-thalassaemia. Br J Haematol. 2007 Feb;136(3):353-65. Epub 2006 Nov 27.

14. Singer ST, Kuypers FA, Olivieri NF, Weatherall DJ, Mignacca R, Coates TD, Davies S, Sweeters N, Vichinsky EP. Single and combination drug therapy for fetal hemoglobin augmentation in hemoglobin E-beta 0-thalassemia: Considerations for treatment. Ann N Y Acad Sci. 2005;1054:250-6.
15. Olivieri NF, Rees DC, Ginder GD, Thein SL, Waye JS, Chang L, Brittenham GM, Weatherall DJ. Elimination of transfusions through induction of fetal hemoglobin synthesis in Cooley's anemia.
Ann N Y Acad Sci. 1998 Jun 30;850:100-9.

Résumés-abstracts

Singer ST, Kuypers FA, Olivieri NF, Weatherall DJ, Mignacca R, Coates TD, Davies S, Sweeters N, Vichinsky EP; E/beta Thalassaemia Study Group. Fetal haemoglobin augmentation in E/beta(0) thalassaemia: clinical and haematological outcome. Br J Haematol. 2005 Nov;131(3):378-88.

Patients with E/beta(0) thalassaemia, the most common haemoglobinopathy in many Asian countries, might benefit from drugs that increase fetal and total haemoglobin and thereby decrease the need for transfusions. The long-term clinical efficacy and safety of such therapy is unknown, limiting its use in countries where resources for safe and regular transfusion are scarce. In this study, 45 patients were treated with hydroxyurea (18-20 mg/kg) for 24+/-9 months, hydroxyurea with sodium phenyl butyrate (n=8) and hydroxyurea with erythropoietin (n=9), each for approximately 6 months, and followed for 3 years from study exit. Hydroxyurea had minimal toxicity, resulted in a mean 1.3 g/dl steady-state increase in haemoglobin in 40% of patients, and a milder response (<OR=1 g/dl) in the others. Baseline haemoglobin F was significantly associated with an increase in haemoglobin (P<0.001). Combined treatment with erythropoietin benefited selected patients, but the addition of sodium phenyl butyrate had no effect. Of the 27/45 patients who discontinued regular transfusions before the study, 13 remained transfusion independent during long-term follow-up, 6/13 continued hydroxyurea. Hydroxyurea moderately increased steady-state haemoglobin in a sub-group of E/beta(0) thalassaemia patients and can be considered for patients with intermediate severity disease, thus delaying or avoiding the need for life-long transfusions. Continuous monitoring of toxicity and growth is required.

Nisli G, Kavakli K, Aydinok Y, Oztop S, Cetingül N, Basak N. Recombinant erythropoietin trial in children with transfusion-dependent homozygous beta-thalassemia. Acta Haematol. 1997;98(4):199-203.

Augmentation of gamma-gene synthesis by using recombinant human erythropoietin (r-Hu-EPO) represents a new approach to the therapy of beta-thalassemia. A prospective study was conducted in 26 transfusion-dependent beta-thalassemia major patients. r-Hu-EPO (Eprex/Cilag, Switzerland) was given to the patients at an initial dose of 500 IU/kg s.c. 3 times a week for at least 2 months during which no transfusion was applied. A sustained hemoglobin (Hb) level greater than 8 g/dl was considered as a response to EPO treatment. In the patients whose Hb levels remained under 8 g/dl or did not increase in comparison to pretreatment levels within 4 weeks, the dose of r-Hu-EPO was increased to 1,000 IU/kg 3 times a week and applied for another 4 weeks. Only 16 cases also received oral iron supplementation. The whole blood and reticulocyte counts, the biochemical tests including BUN, creatinine, AST, ALT, alkaline phosphatase and ferritin were done and the percentages of HbF and F cells were analyzed regularly. At the end of the 2nd month, 6 cases qualified to continue with the trial. At the end of the 6th month, r-Hu-EPO therapy was ceased in 3 cases of the 6 since their Hb levels had decreased below 7 g/dl. Only 3 cases (11.5%) continued with the r-Hu-EPO therapy without transfusion for up to 12 months. In conclusion, r-Hu-EPO may be useful in some selected transfusion-dependent patients with beta-thalassemia major. Selection criteria should include a mild beta-genotype of coinheritance of alpha-thalassemia, splenectomy and pretreatment reticulocyte response of the patients as well as the patients' compliance.

Bencaiova G, Krafft A, Burkhardt T, Breymann C. Variable efficacy of recombinant human erythropoietin in anemic pregnant women with different forms of heterozygous hemoglobinopathy. Acta Haematol. 2006;116(4):259-65.

OBJECTIVE: The aim of this study was to determine the response to recombinant human erythropoietin (rhEPO) in anemic pregnant women with heterozygous hemoglobinopathies. METHODS: A prospective study including 19 consecutive pregnant women with anemia and heterozygous hemoglobinopathy was performed. Treatment was divided into two phases: the initial low-dose phase and the subsequent high-rhEPO phase. In the initial phase, 3 x 10,000 U of rhEPO was administered with intravenous iron sucrose. In patients showing a poor response (Hb increase <1 g/dl) to low-dose rhEPO, the rhEPO dose was increased to 20,000 U per treatment in the subsequent phase. RESULTS: All patients showed stimulation of erythropoiesis as evidenced by an increase in hemoglobin. In 13 patients, a good response to therapy was observed (mean Hb increase 1.6 +/- 0.5 g/dl). In 6 patients, resistance to rhEPO was noted (mean Hb increase 0.5 +/- 0.5 g/dl). The mean gestational age at the start of therapy was 28 weeks of gestation and at the end 32 weeks. The mean duration of a complete therapy was 3.5 weeks (range 2-4.5 weeks). If calculated for body weight, the initial low- rhEPO dose of 160.4 +/- 30.6 U/kg body weight/treatment was increased to 320.9 +/- 61.2 U/kg body weight/treatment in the subsequent phase. CONCLUSION: Response to rhEPO treatment differs widely in anemic pregnant patients with heterozygous

hemoglobinopathy. Resistance was observed in anemic pregnant patients with the beta-thalassemia trait originally from the Mediterranean region.

Nişli G, Kavakli K, Vergin C, Oztop S, Cetingül N. Recombinant human erythropoietin trial in thalassemia intermedia. J Trop Pediatr. 1996 Dec;42(6):330-4.

It has been shown that high doses of human recombinant erythropoietin (r epo) increase haemoglobin levels by augmentation of F-cells, and Hb-F production in animal models and in human trials. In this study, r epo was used in patients with beta thalassemia intermedia. Our purpose was to improve haemoglobin levels by at least 2 g and maintain an average level between 10 and 12 g/dl. Ten patients aged 6-29 years (mean 14 +/- 7.6 years) with thalassemia intermedia were treated with r epo. It was given subcutaneously in rising doses from 500 to 1000 U/kg three times weekly for 3 months. During r epo therapy eight cases (80 per cent) showed an increase in haemoglobin, haematocrit, and reticulocyte levels, and an increase of at least 2 g of haemoglobin was obtained. Blood transfusion was not needed during the study except in one case. Five cases (50 per cent) improved life quality with therapy. Hb levels of all patients returned to baseline values over 1 or 2 months after r epo was discontinued. There was no significant change in absolute Hb-F, F-cells, and ferritin levels during treatment. Generally, the drug was well tolerated. No patient had hypertension. Recombinant erythropoietin seems to be an effective treatment for anaemia of beta-thalassemia intermedia, but longer term randomized trials are needed especially in patients with beta thalassemia major.

Chaidos A, Makis A, Hatzimichael E, Tsiara S, Gouva M, Tzouvara E, Bourantas KL. Treatment of beta-thalassemia patients with recombinant human erythropoietin: effect on transfusion requirements and soluble adhesion molecules. Acta Haematol. 2004;111(4):189-95

The most common single genetic disorder and a major public health issue in Greece and other Mediterranean countries is beta-thalassemia. Current therapeutic approaches for homozygous beta-thalassemia entail blood transfusions and iron chelation therapy with deferoxamine or deferiprone for preventing tissue hemosiderosis. Recently, much effort has focused on various inducers of fetal hemoglobin (HbF) such as recombinant human erythropoietin (rHuEPO), especially in beta-thalassemia intermedia. Ten adult patients, 5 with beta-thalassemia major and 5 with beta-thalassemia intermedia, received 150 IU/kg rHuEPO (epoetin-alpha) subcutaneously three times a week. Seven patients were transfused every 14-30 days and 3 with beta-thalassemia intermedia were only occasionally transfused. The minimum duration of treatment was 12 weeks in order to define if there was any response. Transfusion intervals were modified according to the rHuEPO response to maintain stable Hb values. Lower transfusion requirements were observed in 5 patients after rHuEPO treatment ($p = 0.028$). In the 3 non-transfused patients, Hb values increased, and the patients are still being treated and followed up for a period ranging from 14 weeks to 2 years. Two patients with thalassemia major discontinued treatment after 12 weeks, as they did not achieve any response regarding transfusion requirements or Hb values. Pretreatment serum transferrin receptor levels were higher than in controls ($p < 0.001$) and significantly increased following rHuEPO treatment ($p = 0.027$). Patients had higher serum endothelin-3, sICAM-1 and sE-selectin values before rHuEPO treatment compared to controls ($p < 0.001$, $p < 0.001$ and $p = 0.016$, respectively), but these values were not altered during treatment. HbF values presented a slight, non-significant increase. rHuEPO treatment has a beneficial effect in transfusion-dependent beta-thalassemia patients. Although a slight increase in HbF levels was observed, other possible mechanisms are probably involved. None of our patients experienced thrombotic complications and a rise in blood pressure.

Cozma G. Beneficial use of EPO in sickle cell disease and Thalassaemia intermedia : interim results. Sickle cell disease and Thalassaemia: new trend in therapy. Eds Y Beuzard, B Lubin, J Rosa.1995, vol.234 p207

Rachmilewitz EA. Sustained increase in Hb and RBC following long term administration of EPO to patient with homozygous beta-thalassaemia. Brit J Haema. 1995, 90: 341-5

Bourantas K, Economou G, Georgiou J. Administration of high doses of recombinant human erythropoietin to patients with beta-thalassemia intermedia: a preliminary trial. Eur J Haematol 1997 Jul;59(1):65.

Four patients (1 male, 3 female, age range 16-56 yr) with beta-thalassemia intermedia were given high doses of recombinant human erythropoietin (rHuEpo), iron sulfate and folic acid in an attempt to improve their anemia. The dose schedule was: rHuEpo, 500 U/kg 3 times weekly, iron sulfate, 300 mg/d and folic acid, 5 mg/d. All patients were red blood cell transfusion-dependent. Hematological data and fetal hemoglobin (HbF) were assayed every 2 wk. XmnI polymorphism and beta-thalassemia mutations were identified by PCR. All patients showed a moderate to high increase in hemoglobin values (mean value: 2.5 g/dl) and in 1 patient HbF levels also increased; 3

patients became red blood cell transfusion-independent and 1 patient was able to extend the intervals between transfusions significantly. No side effects were observed during rHuEpo therapy.

Olivieri NF, Freedman MH, Perrine SP, Dover GJ, Sheridan B, Essentine DL, Nagel RL. Trial of recombinant human erythropoietin: three patients with thalassemia intermedia. Blood. 1992 Dec 15;80(12):3258-60

Rachmilewitz EA, Aker M. The role of recombinant human erythropoietin in the treatment of thalassemia. Ann N Y Acad Sci. 1998 Jun 30;850:129-38.

The rationale for treatment with recombinant human erythropoietin (rHuEPO) in thalassemia came from studies in baboons, thalassemic mice and in erythroid cultures. The results demonstrated an increase in gamma globin synthesis and consequently in fetal Hb (Hb F) resulting in improvement in erythropoietic parameters. In addition, endogenous serum Epo levels in various forms of thalassemia were inconsistent and not related to the severity of the anemia. Therefore, several preliminary studies with rHuEPO were performed, mainly on patients with beta thalassemia intermedia. The results indicate: a) a significant, dose-related (500 u/kg to 1000 u/kg x 3/week) increase in thalassemia erythropoiesis without changes in % of Hb F, MCV and MCH, mainly in splenectomized patients; b) the minimum effective dose is 500 u/kg x 3/week; c) there were no major side effects during the continuous treatment period of 9 months. In order to improve both quantitative and qualitative thalassemia erythropoiesis, several trials were undertaken combining rHuEPO with hydroxyurea (HU), which is known to increase % Hb F, MCV and MCH without a major effect on Hb levels. The designed trial included 3 to 6 months of HU alone (20 mg/kg x 4/week), or with rHuEPO alone (500 u/kg x 3/week or 375 u/kg x 2/week) or a combination of the two drugs. The results show an additive effect of the two drugs, in some of the patients. It is not known whether the addition of oral iron to rHuEPO is warranted for maximal erythropoietic response. The major limiting factor in designing large scale clinical trials is the relatively high cost of the drug. Nevertheless rHuEPO alone or in combination with other Hb F modulating drugs may have a positive effect in thalassemia with resulting improvement in the quality of life.

Makis AC, Chaliasos N, Hatzimichael EC, Bourantas KL. Recombinant human erythropoietin therapy in a transfusion-dependent beta-thalassemia major patient. Ann Hematol. 2001 Aug;80(8):492-5.

We report on a 28-year-old patient with transfusion-dependent beta-thalassemia major, who was treated effectively with recombinant human erythropoietin (rHuEpo). rHuEpo promotes the differentiation and proliferation of erythroid cells, induces the production of fetal hemoglobin (HbF), and could be useful in the treatment of some selected transfusion-dependent thalassemia patients. Prior to rHuEpo treatment, the patient was on a regular blood transfusion regimen. Splenectomy did not decrease the transfusion requirements. Additionally, red cell alloimmunization had developed; therefore, we decided to start rHuEpo treatment (Eprex, Jansen Cilag, Greece) in an attempt to improve his anemia and the quality of life. Our patient responded well to rHuEpo treatment and was able to extend the intervals between transfusions from 10-14 to 55-65 days and to sustain a pretransfusion hemoglobin level above 7 g/dl. HbF levels were slightly increased from 55% to 60-65%. Indicators of vascular endothelial activation [serum endothelin-3, intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin] were decreased during treatment. rHuEpo was well tolerated without complications. rHuEpo treatment seemed to have had a beneficial effect and to have improved the quality of life in beta-thalassemia major, although it did have a slight effect on HbF levels, suggesting other possible mechanisms of rHuEpo action.

Perrine SP, Castaneda SA, Boosalis MS, White GL, Jones BM, Bohacek R. Induction of fetal globin in beta-thalassemia: Cellular obstacles and molecular progress.Ann N Y Acad Sci. 2005;1054:257-65.

Accelerated apoptosis of erythroid progenitors in beta-thalassemia is a significant barrier to definitive therapy because the beneficial effects of fetal globin-inducing agents on globin chain balance may not be inducible in cells in which programmed cell death is established early. Accordingly, our objectives have been to identify methods to decrease cellular apoptosis and to identify orally tolerable fetal globin gene inducers. A pilot clinical trial was conducted to determine whether combined use of a fetal globin gene inducer (butyrate) and rhu-erythropoietin (EPO), the hematopoietic growth factor that prolongs erythroid cell survival and stimulates erythroid proliferation, would produce additive hematologic responses in any thalassemia subjects. Butyrate and EPO were administered in 10 patients. Novel fetal globin gene inducers that also stimulate erythroid proliferation were evaluated for pharmacokinetic profiles. Patients with beta+-thalassemia had relatively low levels of endogenous EPO (<145 mU/mL) and had additive responses to administered EPO and butyrate. Patients with at least one beta 0-globin mutation had higher baseline HbF levels (>60%) and EPO levels (>160 mU/mL), and three-fourths of these subjects responded to the fetal globin gene inducer alone. A few select fetal globin-inducing short-chain fatty acid derivatives that stimulated cell proliferation also had favorable pharmacokinetics. These studies identify a significant subset of thalassemia patients who appear to require exogenous EPO to respond optimally to any HbF

inducer, as well as new therapeutic candidates that act on both cellular and molecular pathologies of beta-thalassemia. Both approaches now offer excellent potential for tolerable, definitive treatment of beta-thalassemia.

Quek L, Thein SL. Molecular therapies in beta-thalassaemia. Br J Haematol. 2007 Feb;136(3):353-65. Epub 2006 Nov 27.

The beta-thalassaemias have a major global impact on health and mortality. Allogeneic haemopoietic stem cell transplantation is the only approach that may lead to a cure but this approach is not available to most patients. The mainstay treatment for the majority remains life-long blood transfusion in combination with a rigorous regime of iron chelation. Improved understanding of the pathophysiology and molecular basis of the disease has provided clues for more effective strategies that aim to correct the defect in beta-globin chain synthesis at the primary level or redress the alpha/beta-globin chain imbalance at the secondary level. Improved understanding of the molecular basis of the disease complications, such as iron overloading, has also provided clues for potential molecular targets at the tertiary level.

Singer ST, Kuypers FA, Olivieri NF, Weatherall DJ, Mignacca R, Coates TD, Davies S, Sweeters N, Vichinsky EP. Single and combination drug therapy for fetal hemoglobin augmentation in hemoglobin E-beta 0-thalassemia: Considerations for treatment. Ann N Y Acad Sci. 2005;1054:250-6.

Patients with hemoglobin E (Hb E)-beta 0-thalassemia, one of the most common hemoglobinopathies worldwide, could benefit from drugs that increase fetal and total hemoglobin levels and thereby decrease the need for transfusions. The long-term clinical outcome of such therapy, its hematologic effects, and which patients are likely to benefit from treatment are unknown. Consequently, the use of such drugs for Hb E-beta 0-thalassemia is limited, and countries where resources for safe and regular transfusion are scarce cannot benefit from them. In a multicenter trial of 42 patients treated with hydroxyurea for two years, almost half the patients demonstrated a significant increase in steady-state hemoglobin level. Drug toxicity was minimal. Combined treatment of hydroxyurea with erythropoietin benefited selected patients, but the addition of sodium phenyl butyrate was ineffective. After 5 years of follow-up, a subset of patients remained off transfusions. Hydroxyurea should be considered for a subset of Hb E-beta 0-thalassemia patients.

Olivieri NF, Rees DC, Ginder GD, Thein SL, Waye JS, Chang L, Brittenham GM, Weatherall DJ. Elimination of transfusions through induction of fetal hemoglobin synthesis in Cooley's anemia.Ann N Y Acad Sci. 1998 Jun 30;850:100-9.

Pharmacological stimulation of fetal hemoglobin production is of considerable interest as an alternative approach to therapy for Cooley's anemia. While intravenous compounds have been effective in inducing short-term increases in fetal hemoglobin in a few patients, long-term elimination of transfusion requirement has not been reported. In patients with Cooley's anemia, treatment with oral sodium phenylbutyrate alone, sodium phenylbytyrate combined with hydroxyurea, and hydroxyurea alone, has augmented fetal hemoglobin production and increased total hemoglobin concentration as much as 5 g/dl over baseline eliminating transfusion requirement in two patients. Parallel declines in circulating nucleated red cell count, and concentrations of serum transform receptor and erythropoietin, are consistent with more effective erythropoiesis. Over extended periods of treatment, no induction of other fetal proteins and no adverse effects were observed. Particular disease mutations and other genetic factors may be of prime importance in determining the response to agents that induce production of fetal haemoglobin

- **Drépanocytose**

La drépanocytose, également appelée hémoglobinose S ou anémie à cellules falciformes, est une maladie héréditaire caractérisée par l'altération de la structure de l'hémoglobine qui aboutit à la formation d'hémoglobine S (HbS).
Elle associe 3 grandes catégories de manifestations cliniques, liées :
- à l'anémie hémolytique chronique ;
- aux phénomènes vaso-occlusifs ;
- à la susceptibilité extrême à l'infection,
avec une grande variabilité d'expression clinique selon les individus atteints.

Sous le terme de syndrome drépanocytaire majeur sont regroupées les manifestations cliniques observées en cas :
- d'homozygotie SS ;
- de double hétérozygotie SC, SD, Sβ thalassémique, SO Atab.
Le trait S (patients hétérozygotes AS) sont asymptômatiques.

La drépanocytose est aujourd'hui la plus fréquente des maladies génétiques en France. À l'heure actuelle, on peut estimer entre 6 000 et 7000 le nombre de sujets atteints de syndrome drépanocytaire majeur, avec en France métropolitaine, un nombre supérieur à celui de l'outremer.

Il existe une insuffisance de données publiées pour évaluer l'effet des EPO dans la drépanocytose.

En pratique, certains patients drépanocytaires pourraient bénéficier d'EPO après avis d'un centre de référence :

<u>* Au long cours</u>

- en cas d'aggravation de l'anémie de plus de 2 points par rapport aux taux de base et/ou une concentration d'Hb inférieur à 7 g/dL avec taux d'érythropoïétine sérique bas par rapport à ce qui est attendu compte tenu du taux d'hémoglobine et/ou réticulocytes < 200x 10^9/L, une fois éliminées les autres causes d'aggravation de l'anémie (hémorragie, carence en fer, accentuation de l'hémolyse…). Cette situation correspond le plus souvent à une atteinte rénale débutante sans insuffisance rénale vraie (atteinte tubulaire et/ ou glomérulaire). La clairance de la créatinine définissant l'insuffisance rénale chez un patient drépanocytaire est en dessous de 80ml/mn. Il peut s'agir de patients transfusés au long cours avec une concentration d'Hb pré-transfusionnel bas (inférieur à 7g/dL), ce qui constitue un argument en faveur d'un déficit de production des réticulocytes, d'Hb S et d'érythropoïétine endogène.

- afin d'améliorer la réponse à l'hydroxyurée lorsque le taux d'hémoglobine n'augmente pas suffisamment (moins de 2 points par rapport au taux de base avant traitement). Cette situation est également souvent liée à une atteinte rénale débutante, avec les mêmes arguments biologiques de déficit de production.

Dans toutes ces situations, l'EPO doit être utilisée à doses croissantes de façon prudente, en démarrant par 200U/kg/semaine en SC, en ne dépassant pas habituellement 12 000U/kg/semaine. Une surveillance hebdomadaire est nécessaire au début, et lors des modifications de dose. Il ne faut en effet jamais dépasser une concentration d'hémoglobine de 9-10 g/dL en raison des risques d'hyperviscosité liés à la présence de l'hémoglobine S, et assurer une supplémentation en folates et en fer (sauf si hémochromatose). La darbopoétine (Aranesp) sera utilisée de préférence par voie sous-cutanée.

L'utilisation des EPO dans cette situation concerne environ 1200 patients en France avec un nombre croissant de malades.

* Ponctuellement, en aigu

- en cas d'accident transfusionnel : ces accidents d'hémolyse retardée chez le patient drépanocytaire, qu'ils soient d'origine immunologique prouvée (alloimmunisation complexe) ou non, ont la particularité d'associer un tableau d'hémolyse aiguë intra-vasculaire gravissime (concentration d'Hb chutant rapidement avec déclenchement fréquent de complications vaso-occlusives sévères du fait de la présence d'Hb libre) à un déficit de production (diminution importante du taux de réticulocytes). Une nouvelle transfusion étant souvent périlleuse dans cette situation d'accident transfusionnel, l'utilisation d'EPO à fortes doses peut être utile : les doses sont élevées de l'ordre de 5000 UI/kg au maximum 2-3 fois/semaine jusqu'à l'apparition d'une crise réticulocytaire, avec adjonction systématique de folates.

- en cas d'anémie inflammatoire (syndrome inflammatoire au cours des sepsis, ou complications vaso-occlusives sévères, connectivites…) : l'utilisation d'EPO peut être utile pour réduire les besoins transfusionnels, la transfusion étant dans ces situations peu efficace. Les critères qui doivent guider l'utilisation de l'EPO sont le taux de réticulocytes, le taux d'HbS s'il reste bas après transfusion témoignant d'un déficit de production médullaire.

Effet de l'EPO chez les patients drépanocytaires

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Nagel (1993)	**Randomisée, Double-aveugle versus pla** **N = 9** patients drépanocytaires homozygotes SS	rHuEPO : Gpe 1 : n = 5/9 : 400 à 1500 U/lkg en 2 doses 1j / sem en alternant avec le placebo Gpe 2 : n = 4/9 : idem 1er gpe mais doses 1000 UI à 1500 UI/kg en 2 doses 1j/ sem + Fer (325 mg 3x/ j)	12 sem	Doublement transitoire du taux des réticulocytes F Détermination de la densité des cellules : n = 6	Gpe 1 : pas de réponse à l'EPO 2/5 déficients en Fer Gpe 2 : ↑ taux de réticulocytes F : n = 4/4 répondeurs Effets Indésirables : - 3 phlébites avec ↑ [Hb] > +1.5g/ rapport au niveau de base
El Hazmi (1995)	**Ouverte** **N = 7** patients drépanocytaires 4/7 patients drépanocytaires anémiés 3 Hb S/ β^0-thalassémie	Hu pendant 1 an Puis (dose évaluée individuellement) rHuEPO IV 400 UI/kg/sem. pdt 3-4 sem. + Hu puis Hu seule	13 M	[Hb], [Hb A2), [HbF], [Hte, nombre de cellules F, GR et plaquettes, bilirubine VCM	Hu seule pdt 1 an : Amélioration de l'état clinique des patients - [HbF] et nombre de cellules F: - [Hte], [Hb], GR : ↑ - GB, RBC, bilirubine : ↓ - Plaquettes : valeurs normales EPO + Hu 2/7 : ↓ [HbF] et nombre de cellule 5/ 7 : ↑ [HbF] et nombre de cellul et cette augmentation est mainten après arrêt de l'EPO et après le re au traitement par Hu seule n =2 /7 patients NR au traitement seule mais répondeurs à l'associa Hu + rHuEPO VCM : - pdt traitement par Hu seule et association EPO + Hu : ↑ VCM
Bourantas (1994)	**Ouverte** **N = 6** Hb S/ β^0 - thalassémie	rHu EPO : 500 U/kg sc 2x /sem. pdt 2 sem. puis 3 x /	3 M	- [Hb] et [HbF]	- [Hb] et [HbF] ↑ de 1.25 à 12 fois - bonne tolérance - amélioration clinique : 0 Hosp et

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
		semaine pdt 11 semaines			
Goldberg (1990)	**Ouverte, escalade de dose** **N = 5** Patients drépanocytaires homozygotes SS	rHuEPO IV: en 2 doses 1j/sem . sem 1 et 2 : 2600 UI/kg . sem 3 et 4 : 1100 UI/kg . sem 5 à 8 : 1500 UI/kg 5 à 7 sem post-EPO : 3/5 : Hu : 1x/j Puis après détermination de la dose optimale d'EPO: EPO 1500 UI/kg en 2 doses/j 1j/sem pdt 4 sem + Hu	13 mois	% réticulocytes F % cellules rouges F [Hb F] Effet du Hu	EPO que ce soit seule ou en asso avec le Hu : % de réticulocytes F et de cellules **NS** Hu : réticulocytes F : ↑ 3 à 25 x cellules F : ↑ de 1.6 à 7 x [Hb F] : ↑ de 2.3 à 16 x ↓ taux d'hémolyse et de polymériss intracellulaire de l'HbS
Rodgers (1993)	**Ouverte** **N = 4** patients drépanocytaires 3 Patients homozygotes SS 1 Hb S/ β^0 - thalassémie escalade de dose d'EPO	EPO IV + Fer : + Hu Pdt 7 sem Hu pdt 4 j consécutifs suivis par 3 j d'EPO <u>Phase I :</u> EPO : 1000 UI/kg 1x/sem à 3x/sem <u>Phase II :</u> EPO : 1000 UI/kg à 3000 UI/kg	7 sem	- nombre de réticulocytes F - [Hb F]	EPO + Hu versus Hu seule : **.** ↑ de 28% du nombre de réticulo Contenant de l' HbF **.** ↑ de 48 % [Hb F] . ↑ **%** erythrocytes contenant de l 64 à 78% **.** ↓ taux d'hémolyse
Little (2006)	**Rétrospective** **N = 52 patients** dont n = 42 SS Et n = 10 S /β0 thal . N = 39 patients issus des publications de 1990 à 1996 . N = 13 patients du NIH à partir de 2002	EPO : dose médiane : 200 U/kg/dose	<u>≥</u> 3 mois	- Tolérance - Résultats hématologiques : [HbF], Cellules F, réticulocytes contenant de l'HbF, [Hte]	L'EPO est bien tolérée et recomm chez les patients atteints de drépanocytose en association ave Le traitement par l'EPO permet d' un dosage plus élevé d'Hu chez le patients drépanocytaires à haut ris est une alternative au traitement p chez les insuffisants rénaux ou intolérants à l'Hu

Hu : hydroxyurée
rHuEPO: EPO humaine recombinante
Hb : hémoglobine
Hb F: hémoglobine fœtale
NIH: National Institutes of Health

S/β0 thal : drépanocytaire
GR : globules rouges
GB : globules blancs
VCM : volume cellulaire moyen

Bibliographie

Les référentiels de la Juste prescription du CEDIT (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 1990.

1. Nagel RL, Vichinsky E, Shah M, Johnson R, Spadacino E, Fabry ME, Mangahas L, Abel R, Stamatoyannopoulos G. F reticulocyte response in sickle cell anemia treated with recombinant human erythropoietin: a double-blind study.Blood. 1993 Jan 1;81(1):9-14.
2. el-Hazmi MA, al-Momen A, Kandaswamy S, Huraib S, Harakati M, al-Mohareb F, Warsy AS. On the use of hydroxyurea/erythropoietin combination therapy for sickle cell disease. Acta Haematol. 1995;94(3):128-34.
3. Bourantas KL, Georgiou I, Seferiadis K. Fetal globin stimulation during a short-term trial of erythropoietin in HbS/beta-thalassemia patients. Acta Haematol. 1994;92(2):79-82
4. Goldberg MA, Brugnara C, Dover GJ, Schapira L, Charache S, Bunn HF. Treatment of sickle cell anemia with hydroxyurea and erythropoietin.N Engl J Med. 1990 Aug 9;323(6):366-72.
5. Rodgers GP, Dover GJ, Uyesaka N, Noguchi CT, Schechter AN, Nienhuis AW. Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle cell disease. N Engl J Med. 1993 Jan 14;328(2):73-80
6. Little JA, McGowan VR, Kato GJ, Partovi KS, Feld JJ, Maric I, Martyr S, Taylor JG 6th, Machado RF, Heller T, Castro O, Gladwin MT. Combination erythropoietin-hydroxyurea therapy in sickle cell disease: experience from the National Institutes of Health and a literature review. Haematologica. 2006 Aug;91(8):1076-83.

Résumés-abstracts

Nagel RL, Vichinsky E, Shah M, Johnson R, Spadacino E, Fabry ME, Mangahas L, Abel R, Stamatoyannopoulos G. F reticulocyte response in sickle cell anemia treated with recombinant human erythropoietin: a double-blind study. Blood. 1993 Jan 1;81(1):9-14.

Studies on baboons and preliminary observations in three patients with sickle cell anemia (SS) suggested that high doses of pulse administered recombinant human erythropoietin (rHuEPO) stimulate F-reticulocyte production. We now report on the administration of rHuEPO in a double-blind format to ascertain frequency of response and potential precipitation of side effects. Ten patients were enrolled, but one was discontinued due to the indication of a blood transfusion. Of the other nine, five received rHuEPO in escalating doses (from 400 to 1,500 U per kg twice daily [BID] per week), alternating with a placebo, in blinded fashion. The second group, consisting of four patients, followed an identical protocol (except starting dose was 1,000 U/Kg, BID per week) and were iron supplemented during treatment. The criterion of response was a transient doubling (as a minimum) of the steady-state F-reticulocyte level. We found that none of the five patients in the first group responded to rHuEPO, and two of them became iron deficient, as judged by a significant decrease in ferritin. Of the second group, four patients responded with F-reticulocyte increases. In three patients, open label administration of rHuEPO confirmed the effect. We observed seven painful episodes during this study, two during the EPO administration and five during the placebo arm. Three patients were phlebotomized because the hemoglobin level increased 1.5 g/dL more than steady-state levels. Of the six patients followed-up by percent dense cell determinations, one exhibited increased levels during periods of the treatment, whereas the other five showed no change. No anti-rHuEPO antibodies were detected. We conclude that rHuEPO can stimulate F-reticulocyte response in some patients with sickle cell anemia, without apparent negative clinical side effects. The state of iron stores may be critical. Whether higher doses of rHuEPO and/or a different regimen might induce sustained F cells and fetal hemoglobin increases remains to be determined.

---

el-Hazmi MA, al-Momen A, Kandaswamy S, Huraib S, Harakati M, al-Mohareb F, Warsy AS.
On the use of hydroxyurea/erythropoietin combination therapy for sickle cell disease. Acta Haematol. 1995;94(3):128-34.

Seven sickle cell disease (SCD) patients [sickle cell anaemia = 4 (males 2, females 2, age range 18-40 years), and sickle cell beta (0)-thalassaemia = 3 (all females, age range 20-47 years)], suffering from a severe form of the disease were enrolled in a treatment protocol using hydroxyurea (HU) for up to 12 months followed by a combination therapy with HU and human recombinant erythropoietin (rHuEpo; using 400 U/kg/week i.v.) for 3-4 weeks. Following the withdrawal of rHuEpo the patients were maintained on HU alone. The patients were characterised on the basis of the 'severity index' prior to the initiation of the therapy. Haematological and relevant biochemical parameters, Hb A2 fetal haemoglobin (HbF), HbF cells, reticulocytes and platelet counts were estimated at least at three occasions to determine the mean and range of the parameters. During the treatment period the patients were followed every 2-4 weeks where the haematological and biochemical parameters were assessed. The results were separately analysed and mean +/- SD were obtained for each parameter at the end of each protocol. The statistical significance of the difference in the results obtained on treatment and the baseline results was examined using the paired t test. No toxic side effects of HU and rHuEpo (as judged from reduction in

platelet and white blood cell count) were documented during and after the whole period of treatment. The patients showed a significant clinical improvement. Total haemoglobin, haematocrit, red cell count, HbF and HbF cells increased, while white blood cells, reticulocyte counts and bilirubin level decreased. Platelet count decreased but remained within the normal range. The results revealed that 5 of the patients on HU treatment showed a significant increase in the HbF level and HbF cells, while 2 patients (1 sickle cell anaemia and 1 Hb S/beta(0)-thalassaemia patient) did not and were considered as 'non-responders'. The rHuEpo and HU combination therapy elevated the HbF level, with a varying degree, in all patients except 2, who had already reached a high HbF level and showed a decrease in HbF during the rHuEpo protocol. Variable individual response to both HU and rHuEpo therapy was a common feature. We recommend the use of HU for the treatment of SCD and a combination therapy using HU and rHuEpo for the non-responders.

Bourantas KL, Georgiou I, Seferiadis K. Fetal globin stimulation during a short-term trial of erythropoietin in HbS/beta-thalassemia patients. Acta Haematol. 1994;92(2):79-82

Six sickle cell/beta-thalassemia patients (3 males and 3 females) were treated with 500 U/kg body weight human recombinant erythropoietin (h-rEPO) along with 300 mg/day iron sulfate in two phases, for a period of 90 days. Fetal hemoglobin (HbF) was assayed every 2 weeks and the gamma-chain ratio at three successive intervals during the treatment. All patients showed a moderate to high increase in their HbF values (1.25- to 12-fold). The gamma-chain ratio, as determined by high performance liquid chromatography was found to be unaffected by the HbF increase. Two patients with the newborn gamma-chain ratio, responded faster to the h-rEPO treatment and achieved higher HbF values than the rest of the group. The h-rEPO treatment was very well tolerated and had a positive effect on the general clinical condition of all the patients.

Goldberg MA, Brugnara C, Dover GJ, Schapira L, Charache S, Bunn HF. Treatment of sickle cell anemia with hydroxyurea and erythropoietin.N Engl J Med. 1990 Aug 9;323(6):366-72.

BACKGROUND. Hydroxyurea increases the production of fetal hemoglobin (hemoglobin F) in patients with sickle cell anemia and therefore has the potential for alleviating both the hemolytic and vaso-occlusive manifestations of the disease. There is preliminary evidence that recombinant human erythropoietin may also increase hemoglobin F production. METHODS and RESULTS. We treated five patients with sickle cell disease with escalating doses of intravenous erythropoietin for eight weeks. Three of these patients were subsequently treated with daily doses of oral hydroxyurea. After the optimal dose was determined, erythropoietin was then given along with hydroxyurea for four weeks. Treatment with erythropoietin, either alone or in combination with hydroxyurea, had no significant effect on the percentage of hemoglobin F-containing reticulocytes (F reticulocytes) or red cells (F cells). In contrast, hydroxyurea treatment was associated with a 3-to-25-fold increase in F reticulocytes, a 1.6-to-7-fold increase in F cells, and a 2.3-to-16-fold increase in the percentage of hemoglobin F. In all three patients given hydroxyurea, treatment with this drug was associated with reduced hemolysis, shown by decreases in serum bilirubin and lactic dehydrogenase and prolongation of red-cell survival. Hydroxyurea treatment also resulted in a decrease in the percentage of irreversibly sickled cells and sickling at partial oxygen saturation, an increase in oxygen affinity and total red-cell cation content, and a reduction in potassium-chloride cotransport. All three patients had a decrease in the number of pain crises. CONCLUSIONS. This study confirms that hydroxyurea therapy increases hemoglobin F production and provides objective evidence that hydroxyurea reduces the rate of hemolysis and intracellular polymerization of hemoglobin S. In contrast, recombinant human erythropoietin, whether alone or in combination with hydroxyurea, offers no measurable benefit.

Rodgers GP, Dover GJ, Uyesaka N, Noguchi CT, Schechter AN, Nienhuis AW. Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle cell disease. N Engl J Med. 1993 Jan 14;328(2):73-80

BACKGROUND. Hydroxyurea increases the production of fetal hemoglobin in patients with sickle cell anemia, inhibiting the polymerization of hemoglobin S and potentially improving vaso-occlusive manifestations and hemolysis. Recombinant erythropoietin increases the number of reticulocytes containing fetal hemoglobin in laboratory animals and in humans. We studied whether hydroxyurea and erythropoietin might have a potentiating effect on the production of fetal hemoglobin in patients with sickle cell disease. METHODS. We treated four patients who were receiving hydroxyurea for sickle cell disease (three who were homozygous for sickle cell anemia and one with sickle beta zero-thalassemia) with escalating doses of intravenous erythropoietin for seven weeks, along with oral iron sulfate. Doses of hydroxyurea on four consecutive days were alternated with doses of erythropoietin on three consecutive days. RESULTS. There was a 28 percent increase in the number of reticulocytes containing fetal hemoglobin and a 48 percent increase in the percentage of fetal hemoglobin, as compared with the maximal values obtained with hydroxyurea alone. The percentage of erythrocytes containing fetal hemoglobin (F cells) increased from 64 to 78 percent. As compared with hydroxyurea alone, treatment with hydroxyurea and erythropoietin decreased the mean (+/- SD) serum indirect bilirubin level from 0.8 +/- 0.2 to 0.5 +/- 0.1 mg per deciliter (13.3 +/- 2.9 to 8.9 +/- 2.2 mumol per liter) (P = 0.02), suggesting a further decrease in hemolysis. Red-cell filterability improved. CONCLUSIONS. Intravenous recombinant erythropoietin with iron

supplementation alternating with hydroxyurea elevates fetal-hemoglobin and F-cell levels more than hydroxyurea alone. Such increases decrease intracellular polymerization of hemoglobin S and improve the overall rheologic characteristics of erythrocytes. A reduced dosage of hydroxyurea alternating with erythropoietin may prove less myelotoxic than hydroxyurea given daily or in pulsed-dose regimens. It may also increase levels of fetal hemoglobin in patients with sickle cell disease who have not been helped by hydroxyurea alone.

Little JA, McGowan VR, Kato GJ, Partovi KS, Feld JJ, Maric I, Martyr S, Taylor JG 6th, Machado RF, Heller T, Castro O, Gladwin MT. Combination erythropoietin-hydroxyurea therapy in sickle cell disease: experience from the National Institutes of Health and a literature review. Haematologica. 2006 Aug;91(8):1076-83.

Erythropoietin is being used more widely in the management of sickle cell disease (SCD, inclusive of homozygous sickle beta, SS, and compound heterozygous sickle beta thalassemia, Sbeta0 thal), often in conjunction with hydroxyurea (HU). Herein, we summarize the published experience with erythropoietin use in SCD, in 39 patients (SS, n = 30; Sb0 thal, n = 9) who were treated between 1990 and 1996; and in 13 patients with sickle syndromes (SS, n = 12, compound heterozygous SC disease, n = 1) who were treated with erythropoietin or darbepoietin at the National Institutes of Health (NIH) since 2002. The dose range of erythropoietin for SCD in the published series, at a median of > 200 U/Kg/dose, is higher than that used in end-stage renal disease. The median duration of erythropoietin therapy was > or =3 months, with minimal reported side-effects. At the NIH, the median age of sickle syndrome patients who received erythropoietin or darbepoietin (both referred to as EPO in the NIH series) was 51 (24 to 70) years; 12/13 patients had sickle-associated pulmonary hypertension. Eleven out of the 13 patients were treated with both HU and EPO for > 4 months (median of 11 months on EPO) without complication. Of the 13 patients, five (all SS) with pulmonary hypertension were given EPO for reticulocytopenia (< 100,000/mL) on HU; 5/13 patients (all SS), with pulmonary hypertension, were given EPO and HU concurrently, in the light of an estimated glomerular filtration rate of < 80 mL/minute. Three of the 13 patients (2 SS, 1 SC) were treated with EPO for miscellaneous reasons. Hematologic responses, detailed herein, suggest that EPO therapy may allow more aggressive HU dosing in high-risk SCD patients and in the setting of mild renal insufficiency, common to the aging sickle cell population. Furthermore EPO appears to be safe in SCD, particularly when used in conjunction with HU. We outline our current therapeutic strategy for EPO use in SCD.
Variable efficacy of recombinant human erythropoietin in anemic pregnant women with different forms of heterozygous hemoglobinopathy.

- **Anémie post-transplantation d'organe solide**

➢ **Greffe rénale**

Il n'existe aucune étude randomisée dans les transplantations rénales et les recommandations de la HAS 2005 préconisent l'utilisation d'EPO à distance de la greffe chez les patients en insuffisance rénale chronique (AMM).

Dans les 3 premiers mois post-greffe, les données d'utilisation sont peu solides. L'anémie est constante et multifactorielle : pertes sanguines, syndrome inflammatoire, retard dans l'amélioration de la fonction rénale, infections, rejet aigu.
Les résultats de 2 études randomisées en post-transplantation immédiate, dont une avec des doses élevées d'EPO, seront bientôt disponibles.

Après 3 mois, l'anémie est souvent liée à une insuffisance rénale et/ou à certains médicaments immunosuppresseurs tels que l'azathioprine, le mycophénolate mofétil (MMF) ou les inhibiteurs du système Rénine-Angiotensine.
Il est à noter que la définition de l'insuffisance rénale chez les patients transplantés rénaux est difficile : Clairance de la créatine < 60 ml/min (environ).

Une seule étude rétrospective à long-terme (Lietz 2003) montre que l'EPO permet une augmentation de l'Hb (cible déterminée = 11-12 g/dL), et suggère que la qualité de vie et la survie du greffon sont améliorées, de même que la survie des patients.

Une étude est en cours sur 2 ans (cible [Hb] = 13 g/dl) ; les résultats à 1 an montrent une amélioration de la qualité de vie.

➢ **Greffe cardiaque**

Au cours de la phase initiale post-transplantation, les données sont insuffisantes pour évaluer le bénéfice/risque d'un traitement par EPO. Les résultats des études randomisées en cours sont attendus.
A distance de la greffe, la situation ne relève plus d'un PTT mais de l'AMM puisque les patients sont en insuffisance rénale.

Effet de l'EPO dans l'anémie des patients transplantés

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Campise (2005)	**Ouverte** **N = 15 051** transplantés rénaux	rHuEPO débutée avant la transplantation et les patients sont divisés : - répondeurs - répondeurs partiels	24 mois	Répondeurs à l'EPO : [Hb] ≥ 11 g/dL Répondeurs partiels: rHuEPO : >300 UI /kg/sem sans ↑ de l'Hb et [Hb] < 11g/dL De la transplantation : - au rejet de greffe : % de rejets de greffes - au décès : % des décès	Résultats cumulés à 5 ans : - répondeurs : 14703 (97%) - répondeurs partiels : 348 (3%) Rejet greffe : * Incidence des rejets de greffes cumulés sur 60 mois - 50% des patients répondeurs partiels à l'EPO - 41.7% des répondeurs (**p = 0.0091)** * Taux d'échec des greffes : 9.71% des patients répondeurs versus 11.91% des patients non-répondeurs Dialyse ou retransplantation : - 41, 7% des répondeurs partiels - 32% des répondeurs (**p = 0.0091)** Décès avec un greffon actif :

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
				- à la retransplantation ou retour à la dialyse : %	-16.9% chez les répondeurs partiels - 15 % chez les répondeurs (**NS)**
Linde (2001)	**Ouverte** **Randomisée** Insuffisants rénaux anémiés **N = 56** transplantés prétraités par EPO Gpe 1 : [Hb] = 13.5-16 g/dlL (n = 32) Gpe2 : [Hb] = 9-12 g/dL (n= 24)	EPO : dose ?	1 an	[Hb] Patients nécessitant des transfusions de sang Activité des greffons CRP	[Hb] avant transplantation: Gpe 1 : 14.3 g/dL+- 1.7 Gpe 2 **:** 12.1 g/dL +- 1.4 **(p < 0.0001)** A S2 post-transplantation : [Hb] > gpe 1 versus gpe 2 A M3, M6 : [hb] gpe 1 = [Hb] gpe 2 Patients nécessitant des transfusions en post-transplantation : Gpe 1 : 16% Gpe 2 : 50 % (**p < 0.01)** % de greffons fonctionnant correctement : **NS** CRP **: NS** Bonne tolérance dans les 2 groupes
Fernandez-Lucas (1996)	**Ouverte** **N = 91** patients transplantés rénaux dialysés	rHuEPO: n = 42 dose minimale : 50 UI/kg 3x / sem avant transplantation Contrôles : n = 49		eEPO [Hb] [Hte] Créatinine sérique A J0, J2, J4, J8, J15, J30, J60 et J180 post-transplantation Ferritine : avant transplantation et J60 post-transplantation	Patients non traités versus patients traités par EPO avant la transplantation: **.** ↑ eEPO transitoire : **p< 0.001** . Correction de l'anémie post-transplantation : **NS** . Pic eEPO : **NS** quel que soit le temps de récupération de la fonction rénale Patients traités avec reprise rapide de la fonction rénale versus reprise retardée : [Hte] prétransplant : **NS**: Patients non traités : [Hte] prétransplant avec reprise de la fonction rénale < [Hte] avec reprise retardive de la fonction rénale : [Hte] : ↓ **S (p < 0.05)** Temps de récupération de la fonction rénale : non lié au taux d'eEPO Reprise de la fonction rénale retardée : - 52% patients traités - 36% patients non traités Pas d'effet de la rHuEPO pdt la dialyse chez les patients dont la fonction rénale récupère tardivement
Ribes (2008)	**Ouverte** **monocentrique** **N = 56** patients transplantés rénaux depuis plus de 3 mois avec anémie non ferriprive et IRC	Darbepoetin alfa (DA) sc: dose pour [Hb] =11-13 g/dl <u>Gpe 1</u> : non prétraités par rHuEPO (n = 33) <u>Gpe 2 :</u> prétraités par rHuEPO	9 mois	[Hb] : entre J0 et 6 mois Dose de DA nécessaire A M3 et M6	<u>A M6</u> : - Gpe 1 (non prétraités par rHuEPO) : **.** ↑ [Hb] de +1.27 g/dl (IC 95 : 0.61-1.94) **.** ↓ Dose de DA de 44% - Gpe 2 (prétraités) : **.** ↑ [Hb] de +0.63g/dl (IC 95% : -0.16, 1.14) . Dose de DA inchangée

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
		(n = 23)			
Ortiz (2003)	**Ouverte** **N = 50** patients transplantés rénaux Créatine plasmatique Gpe A : < 150 µmol/L Gpe B : 150-250 µmol/L Gpe C : > 250 µmol/L	rHuEPO (en moyenne) <u>Gpe A</u> : 3000 UI sc <u>Gpe B</u> : 4000 Sc <u>Gpe C</u> 7500 IU sc	1 an	Temps pour atteindre : [Hb] > 12g/dl CRP Protéinurie Nombre de médicaments antihypertenseurs	- Temps pour atteindre la cible [Hb] > 12g/dl : . Gpe A : 2 mois . Gpe B : 3 mois . Gpe C : 6 mois - Le traitement par EPO ne modifie pas la fonction rénale, la protéinurie ni le nombre de médicaments anti-hypertenseurs (IEC et ACII) - L'atteinte rénale détermine le temps nécessaire pour atteindre [Hb] > 12g/dL et la dose d'EPO nécessaire - L'utilisation des IEC et des IAII augmente les besoins en EPO
Lezaic (1995)	**Ouverte, comparative** **N = 45** Gpe A : IRC du greffon (n = 8) Gpe B : patients en prédialyse (n = 20) Gpe C : patients en hémodialyse (n = 17)	rHuEPO 150 UI/kg/sem Dose augmentée de 25 UI/kg si [Hb] de 10 g/dl n'est pas atteinte en 4 sem Doses d'EPO maintenues pour que [Hb] = 10 g/dL Fer PO pour les patients non polytransfusés et pour tous les patients en prédialyse		[Hb] Réponse au traitement pour atteindre la cible de [Hb] (10g/dL)	Correction de l'anémie : 45/45 en 2 à 10 sem de traitement Meilleure réponse chez les patients ayant des valeurs d' [Hb] très faibles Pendant la phase initiale du traitement : ↑ **S** [Hb] + rapide dans les gpes A et B versus gpe C Effet de l'EPO + important si fonction rénale conservée Progression de l'IRC du greffon du gpe A et gpe B : **NS** L'amélioration de l'anémie n'accélère pas la progression de la fonction rénale du greffon
Van Biesen (2005)	**Ouverte comparative** **N = 40** patients anémiés En post-transplantation - patients traités par EPO : n = 22 - patients non traités par EPO : n = 18	rHuEPO (NéoRecormon) : 100 U/kg 3 x/sem si [Hb] < 12.5g/dL		Réponse à l'EPO : [Hb] ≥ 11 g/dL Temps pour atteindre [Hb] > 12.5g/dL Taux de créatinine sérique	Réponse : **NS** - Gpe EPO = 14/22 (64%) - Contrôles : 12/18 (67%) Temps pour que [Hb] > 12.5 g/dL : - Gpe EPO = 53 +/- 24 j - Contrôles : 66 +/- 14 j **S (p = 0.05)** [Hb] à M3 : - Gpe EPO = 12 g/dL - Contrôles : 12,6 g/dL **NS** Taux de créatinine sérique : **NS**
El Haggan (2004)	**Ouverte** **N = 24** patients transplantés rénaux	Darbepoetin alfa 0.45 µg/kg s.c : 1x/sem pdt 6 mois jusqu'à la cible [Hb] > 12 g/dL puis dose de DA ajustée Autres traitements :		[Hb] : 12 - 13.5 g/dL CRP Ferritine Transferrine Protéinurie/24h	[Hb] : ↑**S** de +1.3+/- 0,6 g/dl (**p = 0.0002)** Clairance de la créat et protéinurie des 24h : **NS** Bonne tolérance du traitement

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
		immunosuppresseurs IAII			
Baltar (2007)	**Ouverte :** **N = 24** patients transplantés atteints d'une néphropathie chronique du greffon et anémie non ferriprive	rHuEPO sc : 2000 UI/sem puis ↑ de la dose de 2000 UI toutes les 4sem avec un maximum de 12000 UI/sem		[Hte] : 35% [Hb] ≥ 11 g/dL	A M4 : - correction de l'anémie : 86% - survie du greffon : 71% - effets indésirables : 19% - patients avec fonction rénale du greffon normale montre une correction de l'anémie: p = 0.001 - patients dont l'anémie n'est pas corrigée ont une fonction rénale du greffon dégradée: p = 0.028
Nampoory (1996)	**Ouverte** **N = 23** transplantés rénaux avec une fonction rénale normale Gpe 1 : [Hb] et [Hte] normales : n = 11 : contrôles Gpe 2 : n = 12 patients anémiés dont 5 patients ont été suivis jusqu'à la fin de l'étude	rHuEPO : (5 patients du gpe 2) 50 U/kg/sem s.c. puis dose augmentée de 25 UI/kg toutes les 2 sem si [Hb] et [Hte] non améliorées	9-12 mois	[Hb] et [Hte] eEPO et sEPO	Gpe 1 : - eEPO normal : n = 5 - eEPO élevé (résistance à l'EPO) : n = 6 Gpe 2 Avant traitement sEPO bas : n = 3 sEPO élevé : n = 2 Après traitement : 3/5 déficients en EPO : [Hb] et [Hte] normales en 4 sem. 2/5 EPO résistants ont nécessité 11 sem de traitement Après arrêt du traitement : ↓ [Hb] et [Ht] en 6 mois : n = 5/5
Gleissner (2006)	**Ouverte** **N = 12** patients anémiés ([Hb] < 12g/dL) post-transplantation cardiaque et IR	EPO : époétine bêta : 4000 UI 1-3 x /sem pdt 3 mois	6 mois	[Hb] sEPO Qualité de vie	[Hb] : ↑ **S** (p < 0.005) - prétraitement : 10.8 ± 1.1 g/dL - à M3 : 14.1 ± 1.7 g/dL - après 3 mois d'arrêt de traitement : valeurs similaires aux valeurs avant traitement QdV: ↑ **S:** 8/ 12 (75%)
Lietz (2003)	**Rétrospective** **N = 502** transplantés rénaux pour la 1ère fois et dont la greffe a survécu > 6 mois - Gpe 1 : patients prétraités (n = 51) - Gpe 2 : patients transfusés (n = 207) - Gpe 3 : patients transfusés puis switchés vers EPO (n = 184) - Gpe 4 : pas de traitement (n = 60)	rHuEPO	5 ans	% de PRA avant transplantation Fréquence des rejets Survie du greffon	% de PRA avant transplantation : - Nbre de patients très sensibilisés (PRA > 20%) versus contrôles : ↓ **S**de 32% à 17% **(p < 0.001)** **-** Temps d'attente jusqu'à la greffe versus contrôles : **↓ S (p< 0.001)** Rejet de greffe : - à 1 an : **NS** - à 5 ans : **p < 0.001** . Gpe 1 : 7% . Gpes 2 et 3 : 22% . Gpe 4 : 18 % Rejets tardifs : **-** Gpe 1: ↓ 0.42 à 0.27 **(p = 0.03)**

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Mohiuddin (2007)	**Rétrospective** **N = 182** patients transplantés rénaux - patients recevant un traitement EPO juste après la transplantation et pdt 6 mois - patients ne recevant pas d'EPO	rHuEPO + Immunosuppresseurs et corticoïdes	6 mois	[Hb] Créat J7, J14, J30, J60 et J90	[Hb] : ↓ **NS** - prétransplantation : 12.4 ± 1.6 g/dL - à J 14 : 9.5 ± 1.5 g/dL - à J 30 : 10.5 ± 1.6 g/dL - à J 90 : 12.4 ± 1.7 g/dL Créat avant transplantation puis à J14, J30 et J90 : ↓ **NS** L'utilisation d'EPO pdt les 3 premiers mois post-transplantation n'a pas d'effet sur l'anémie et le délai de reprise de la fonction rénale
Nagarajan (2007)	**Rétrospective** **N = 100** enfants transplantés rénaux **:** - enfants ne nécessitant pas de corticoïdes (n = 50) - enfants sous corticoïdes (= contrôles : n = 50)	rHuEPO	2 ans	- Incidence de l'anémie - Doses d'EPO - Incidence d'une hypertension et d'anomalies réno-vasculaires	<u>A 1an post-transplantation</u> : Gpe sans corticoïdes versus gpe contrôle : - incidence de l'anémie + élevée : **p < 0.001** - dose d'EPO + élevée - incidence + faible de l'hypertension et des anomalies réno-vasculaires : **p = 0.03** - utilisation d'EPO dès la 1ère sem post-transplantation : . incidence + élevée de nouveaux cas d'HTA (**p = 0.03**) et d'anomalies réno-vasculaires (**p = 0.007**) Gpe contrôle versus gpe sans corticoïdes : - Sous corticoïdes, l'utilisation d'EPO est associée à 100% avec la survenue d'HTA et d'anomalies rénovasculaires : **p < 0.001**
Mc Devitt (2005)	**Rétrospective** **N = 36** < 3 mois post-transplantation : 50% des patients > 12 mois post-transplantation : 44% :	Darbepoetin alfa Autres traitements avant darbépoïétine : - rHuEPO : 19% - IEC : 47% - tacrolimus : 53% - ciclosporine : 44%	12 sem	[Hb] > 12g/dL	A S4 : Répondeurs : 81% Pas d'influence de la durée de l'anémie, de l'origine du greffon, des autres traitements ni de l'état de la fonction rénale sur le % de répondeurs, temps de réponse, besoins d'EPO Patients anémiés > 12 mois post-transplantation et /ou sous IEC : ↑ temps pour atteindre [Hb] > 12g/dL Bonne tolérance
Kessler (1995)	**Revue**	L'anémie post-transplantation doit être corrigée pdt 8-10 sem rHuEPO : ↓ des transfusions de sang ⇒ - chez des patients non sensibilisés (grossesse, greffe préalable) :↓ des sensibilisations anti-HLA. - chez les patients présensibilisés : ↓ niveau de sensibilisation - prévention des érythrocytoses post-transplantation si utilisation des EPO avant la transplantation			

CRP: C-reactive protein PRA: panel reactive antibody IR : insuffisance rénale eEPO : EPO endogène [Hte] : hématocrite

IEC : inhibiteurs de l'enzyme de conversion
IRC : insuffisance rénale chronique
Creat : créatinine
IAII : inhibiteurs de l'angiotensine II

Bibliographie

Les référentiels de la Juste prescription du CEDIT (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 1995.

1. Campise M, Mikhail A, Quaschning T, Snyder J, Collins A. Impact of pre-transplant anaemia correction and erythropoietin resistance on long-term graft survival. Nephrol Dial Transplant. 2005 Sep;20 Suppl 8:viii8-12.
2. Linde T, Ekberg H, Forslund T, Furuland H, Holdaas H, Nyberg G, Tydén G, Wahlberg J, Danielson BG. The use of pretransplant erythropoietin to normalize hemoglobin levels has no deleterious effects on renal transplantation outcome.Transplantation. 2001 Jan 15;71(1):79-82
3. Fernández Lucas M, Marcén R, Villafruela J, Teruel JL, Tato A, Rivera M, Ortuño J. Effect of rHuEpo therapy in dialysis patients on endogenous erythropoietin synthesis after renal transplantation. Nephron. 1996;73(1):54-7
4. Ribes D, Kamar N, Guitard J, Esposito L, Rostaing L. Darbepoetin-alfa in renal-transplant patients: an observational monocentric study. Clin Nephrol. 2008 Feb;69(2):102-6
5. Ortiz F, Guirado L, Díaz J, García-Trabanino R, Garra N, Sáinz Z, Picazo M, García RM, Alcaraz A, Solà R. Use of recombinant human erythropoietin in kidney transplant patients with stable graft function. Transplant Proc. 2003 Aug;35(5):1767-8.
6. Lezaic V, Djukanovic L, Pavlovic-Kentera V. Recombinant human erythropoietin treatment of anemia in renal transplant patients. Ren Fail. 1995 Nov;17(6):705-14.
7. Van Biesen W, Vanholder R, Veys N, Verbeke F, Lameire N. Efficacy of erythropoietin administration in the treatment of anemia immediately after renal transplantation. Transplantation. 2005 Feb 15;79(3):367-8.
8. El Haggan W, Vallet L, Hurault de Ligny B, Pujo M, Corne B, Lobbedez T, Levaltier B, Ryckelynck JP. Darbepoetin alfa in the treatment of anemia in renal transplant patients: a single-center report. Transplantation. 2004 Jun 27;77(12):1914-5
9. Baltar J, Moran N, Ortega F, Ortega T, Rebollo P, Cofan F, Campistol JM. Erythropoietin safety and efficacy in chronic allograft nephropathy. Transplant Proc. 2007 Sep;39(7):2245-7
10. Nampoory MR, Johny KV, al-Hilali N, Seshadri MS, Kanagasabhapathy AS. Erythropoietin deficiency and relative resistance cause anaemia in post-renal transplant recipients with normal renal function. Nephrol Dial Transplant. 1996 Jan;11(1):177-81
11. Gleissner CA, Klingenberg R, Staritz P, Koch A, Ehlermann P, Wiggenhauser A, Dengler TJ. Role of erythropoietin in anemia after heart transplantation. Int J Cardiol. 2006 Oct 10;112(3):341-7.
12. Lietz K, Lao M, Paczek L, Górski A, Gaciong Z. The impact of pretransplant erythropoietin therapy on late outcomes of renal transplantation. Ann Transplant. 2003;8(2):17-24.
13. Mohiuddin MK, El-Asir L, Gupta A, Brown A, Torpey N, Ward M, Talbot D, Ahmed S. Perioperative erythropoietin efficacy in renal transplantation. Transplant Proc. 2007 Jan-Feb;39(1):132-4.
14. Nagarajan S, Mansfield E, Hsieh S, Liu R, Hsieh F, Li L, Salvatierra O Jr, Sarwal MM. Transplant reno-vascular stenoses associated with early erythropoietin use. Clin Transplant. 2007 Sep-Oct;21(5):597-608.
15. McDevitt LM, Smith LD, Somerville KT, Corbett JL, Shihab FS. A retrospective assessment of pre-treatment variables on the response to darbepoetin alfa after renal transplantation. Am J Transplant. 2005 Aug;5(8):1948-56.
16. Kessler M. Erythropoietin and erythropoiesis in renal transplantation. Nephrol Dial Transplant. 1995;10 Suppl 6:114-6.
17. Goodnough LT. The role of iron in erythropoiesis in the absence and presence of erythropoietin therapy. Nephrol Dial Transplant. 2002;17 Suppl 5:14-8.

Résumés-abstracts

Campise M, Mikhail A, Quaschning T, Snyder J, Collins A. Impact of pre-transplant anaemia correction and erythropoietin resistance on long-term graft survival. Nephrol Dial Transplant. 2005 Sep;20 Suppl 8:viii8-12.

BACKGROUND: This study investigated whether recombinant human erythropoietin (rHuEPO)-hyporesponsive anaemia before transplantation is associated with a poorer graft outcome and lower patient survival. METHODS: A total of 15,051 kidney transplant recipients, with a minimum follow-up of 1 year, were stratified as either rHuEPO hyporesponsive or rHuEPO responsive (using a threshold rHuEPO-treated haemoglobin level of 11 g/dl). They were followed for a median of 24 months. Outcomes included times from transplantation to graft failure (including patient death), return to dialysis or pre-emptive re-transplantation, and death with a functioning graft. RESULTS: The cumulative incidence of graft failure was 50% for rHuEPO-hyporesponsive patients, compared with 41.7% for rHuEPO responders (P = 0.0091). Among rHuEPO-hyporesponsive patients, 41.7% returned to dialysis or underwent a pre-emptive re-transplantation, compared with 32% of rHuEPO responders (P = 0.0091). Death with a functioning graft occurred in 16.9% of rHuEPO-hyporesponsive and in 15% of rHuEPO-responsive patients (P = 0.3949). CONCLUSIONS: The results showed higher mortality and higher incidence of graft failure at 5 years for rHuEPO-hyporesponsive patients. It is unclear whether anaemia treatment per se or treatment of more severe co-morbidity resulting in hyporesponsiveness to anaemia treatment may be causally linked to reduced renal transplant outcomes.

Linde T, Ekberg H, Forslund T, Furuland H, Holdaas H, Nyberg G, Tydén G, Wahlberg J, Danielson BG. The use of pretransplant erythropoietin to normalize hemoglobin levels has no deleterious effects on renal transplantation outcome.Transplantation. 2001 Jan 15;71(1):79-82

BACKGROUND: The aim of this study was to establish the outcome of renal transplantation in patients given pretransplant erythropoietin (EPO) treatment targeted at reaching a normal hemoglobin concentration (Hb), compared to those given EPO-treatment aimed at maintaining subnormal Hb. METHODS: A total of 416 patients from Scandinavian countries and with renal anaemia were enrolled to examine the effects of increasing Hb from a subnormal level (90-120 g/liter) to a normal level (135-160 g/liter) by EPO treatment. Half of the patients were randomized to have their Hb increased, with the other half randomized to maintain a subnormal Hb. Thirty-two patients from the normal Hb group and 24 patients from the subnormal group received a renal graft during the study period. The outcomes of these transplantations were examined prospectively for 6 months. RESULTS: Preoperative Hb levels were 143+/-17 and 121+/-14 g/liter in the two groups, respectively (P<0.0001). The Hb remained higher in the normal Hb group during the first 2 weeks after transplantation. The percentage of patients requiring postoperative blood transfusions in the normal Hb group was 16%, compared with 50% in the subnormal group (P<0.01). No statistically significant difference in the proportion of functioning grafts or in the serum creatinine levels could be detected. No correlation between EPO treatment and creatinine levels after transplantation was found. The frequency of adverse events was similar in the two groups. CONCLUSIONS: EPO treatment aimed at reaching a normal Hb in renal transplant recipients reduces the postoperative requirement for blood transfusions and has no deleterious effects on kidney graft function.

Fernández Lucas M, Marcén R, Villafruela J, Teruel JL, Tato A, Rivera M, Ortuño J. Effect of rHuEpo therapy in dialysis patients on endogenous erythropoietin synthesis after renal transplantation. Nephron. 1996;73(1):54-7

We have undertaken a prospective study to examine the effect of recombinant human erythropoietin (rHuEpo) therapy during dialysis on Epo levels after renal transplantation and to evaluate the impact of this therapy on the immediate graft function. Between December 1991 and December 1993, 91 renal transplant recipients were studied. There were 34 females and 57 males and the mean age was 38 years. Forty-two patients were treated during dialysis with rHuEpo due to anemia and 49 patients did not receive it. Endogenous Epo (eEpo), hemoglobin concentration, hematocrit level and serum creatinine were determined on days 0, 2, 4, 8, 15, 30, 60 and 180 after transplantation. Ferritin level was determined pretransplant and on day 60. Results: Patients not treated with rHuEpo during dialysis experienced a transient increase in endogenous Epo after renal transplant that was not observed in treated patients (26 +/- 3.3 vs. 9 +/- 1.5 mU/ml, p < 0.001). The eEpo peak was similar in patients with early or delayed graft function (23 +/- 4.3 vs. 32 +/- 5.4 mU/ml, NS). The recovery of the anemia after a successful renal transplant took place in patients treated as well as those not treated with rHuEpo without significant differences. In the treated group, the pretransplant hematocrit level was similar in patients with early or delayed graft function (31 +/- 3.5% vs. 32 +/- 4.8%), but in the untreated group, the hematocrit level was lower in patients with early renal function (28.5 +/- 4% vs. 32 +/- 3%, p < 0.05). However, these patients also had a significantly shorter warm ischemia time (53 +/- 13.8 vs. 64 +/- 14.5 min). Fifty-two percent of the rHuEpo-treated patients and 36% of the untreated patients had delayed graft function. In conclusion, different courses of eEpo levels after renal transplant were observed depending on whether or not patients had been treated with rHuEpo during dialysis. Untreated patients experienced a transient increase which was not observed in the treated group. Immediate or delayed graft function did not modify eEpo levels. No association was found between rHuEpo therapy during dialysis and delayed graft function.

Ribes D, Kamar N, Guitard J, Esposito L, Rostaing L. Darbepoetin-alfa in renal-transplant patients: an observational monocentric study. Clin Nephrol. 2008 Feb;69(2):102-6

BACKGROUND: Anemia, frequent in post-transplant patients, has been associated with cardiovascular outcomes. Although recombinant human erythropoietin (rHuEPO) is used in post-transplant anemic patients, little information is available concerning the use of darbepoetin-alfa (DA) in this population. METHODS: Eligible patients had been recipients of a kidney graft for > 3 months, had anemia and chronic renal failure, but no iron deficiency. 38 patients, not previously treated by rHuEPO (Group 1), were given DA, and 35 rHuEPO-treated patients (Group 2) were switched to DA according to European Summary of Product Characteristics. Only the subcutaneous route was used. Dose adjustments were done to maintain Hb at 11 - 13 g/dl. Hb levels and DA dosage were assessed at baseline, and at Months 3 and 6. RESULTS: Mean age (A+/- SD) of patients was 47.7 (A+/- 13.4) years (53% male). Mean duration of transplantation was 8.5 (A+/- 5.5) years and mean creatinine clearance was 42.5 (A+/- 19.8) ml/min. In Group 1, mean Hb became increased by +1.27 g/dl (95% CI 0.61, 1.94) and mean DA dose was decreased by 44% between baseline and M6. In Group 2, mean Hb and DA dose remained stable between baseline and M6. Hb response to DA appeared faster in patients who had received a transplant for less than 3 years, and lower in patients who had received a transplant more than 12 years previously. CONCLUSIONS: DA effectively corrected anemia in renal-transplant patients, in previously treated patients and in EPO-naive patients. DA was also found to be well-tolerated.

Ortiz F, Guirado L, Díaz J, García-Trabanino R, Garra N, Sáinz Z, Picazo M, García RM, Alcaraz A, Solà R. Use of recombinant human erythropoietin in kidney transplant patients with stable graft function. Transplant Proc. 2003 Aug;35(5):1767-8.

The purpose of this work was to determine the necessity for rhuEPO for 50 kidney transplant patients with stable graft function. We analyzed the red cell series, blood pressure, renal function, anthropometric data of the donor and recipient, proteinuria, and relationship with other factors, including immunosuppressants, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB). The patients were divided into three groups depending on renal function: group A (with plasma creatinine <150 micromol/L), group B (151-250 micromol/L), and group C (>250 micromol/L). All patients were studied for 1 year. Erythropoietin use did not affect renal function, proteinuria or number of antihypertensive drugs group. The degree of renal dysfunction determined the time necessary to reach an adequate hemoglobin level (>12 g/L) and and the mean dose of weekly rhuEPO needed. The use of ACE inhibitors or ARBs increased the rhuEPO requirements in each group.

Lezaic V, Djukanovic L, Pavlovic-Kentera V. Recombinant human erythropoietin treatment of anemia in renal transplant patients. Ren Fail. 1995 Nov;17(6):705-14.

The rHuEpo effect on anemia in eight renal transplant patients (group A) with severe anemia (Hb 6.0-7.5 g/dL) and chronic graft failure (CGF) (sCr 281-794 mumol/L) was compared to the rHuEpo effect on anemia in predialysis (20 patients-group B) and hemodialysis patients (17 patients-group C) in order to examine the rHuEpo effect on anemia and graft failure progression, and to find out whether the response to therapy in these three patient groups differed. Although renal function impairment was similar in patients from group A and B, anemia was more severe in patients from group A. Serum immunoreactive erythropoietin levels were within normal limits for nonanemic persons, that is, inadequate for the level of anemia in all patients before therapy. Maintenance immunosuppression given after renal transplantation consisted of cyclosporine, azathioprine, and prednisone in standard doses. The startig rHuEpo dose of 150 U/kg/wk increased by 25 U/kg if the target Hb of 10.0 g/dL was not achieved at the end of a 4-week period. When target Hb was achieved, the rHuEpo dose was regularly adjusted to maintain Hb of 10.0 g/dL. Most patients from group A and group C were polytransfused before rHuEpo therapy and consequently with iron overload so that only some patients from these groups and all predialysis patients needed iron supplementation given orally. Anemia improved in all patients with 2 to 10 weeks of treatment. Mean rHuEpo doses for the first 2 months were similar in three studied groups, but the patients with the lowest initial hemoglobin values responded better to rHuEpo therapy. The rate of Hb increase during the initial phase of therapy was significantly higher in patients from group A and B comparing to patients from group C, indicating the importance of residual renal function for rHuEpo effect on anemia. Progression of CGF expressed by the slope of l/sCr vs. time did not change in either patient from group A or in predialysis patients. It could be concluded that rHuEpo therapy improved anemia in transplant patients as in predialysis and hemodialysis patients. Anemia improvement by rHuEpo did not accelerate the progression of graft function.

Van Biesen W, Vanholder R, Veys N, Verbeke F, Lameire N. Efficacy of erythropoietin administration in the treatment of anemia immediately after renal
transplantation. Transplantation. 2005 Feb 15;79(3):367-8.

Anemia negatively impacts cardiovascular comorbidity and hospitalization. In animals, recombinant erythropoietin (RhuEPO) leads to faster recovery after acute tubular necrosis. This study evaluates the effect of RhuEPO (Recormon, Hoffman-La Roche, Basel, Switzerland) on the correction of anemia and kidney function after renal transplantation. Patients receiving a renal transplant were randomized to receive or not receive RhuEPO 100 U/kg three times per week if the hemoglobin (Hb) level was less than 12.5 g/dL. The time to reach an Hb level greater than 12.5 g/dL was 66.5+/-14.5 days versus 52.6+/-23.7 days in the non-EPO and EPO groups, respectively (P=0.05). After 3 months, Hb levels were not different between the non-EPO and EPO groups (12.6+/-1.5 g/dL vs. 12.0+/-1.5 g/dL, respectively), although there was a higher increase in the EPO group (4.1+/-1.1 g/dL vs. 3.2+/-1.1 g/dL, P=0.02). In a Cox regression analysis, EPO use (relative risk 7.2, P=0.004) and dose (relative risk=0.63, P=0.04) were retained as independent variables predicting the time to reach an Hb level greater than 12.5 g/dL. In the EPO group, 14 of 22 patients reached the target Hb level of more than 12.5 g/dL versus 12 of 18 patients in the non-EPO group (P=not significant). Serum creatinine levels were not different between groups. RhuEPO in the immediate posttransplantation period seems to have no relevant clinical impact on the correction of anemia. There was no difference in the evolution of serum creatinine levels. In view of the cost, the use of RhuEpo in the posttransplantation period should be limited to high-risk patients.

El Haggan W, Vallet L, Hurault de Ligny B, Pujo M, Corne B, Lobbedez T, Levaltier B, Ryckelynck JP. Darbepoetin alfa in the treatment of anemia in renal transplant patients: a single-center report. Transplantation. 2004 Jun 27;77(12):1914-5 : no abstract

---

Baltar J, Moran N, Ortega F, Ortega T, Rebollo P, Cofan F, Campistol JM. Erythropoietin safety and efficacy in chronic allograft nephropathy. Transplant Proc. 2007 Sep;39(7):2245-7

BACKGROUND: Patients with chronic allograft nephropathy (CAN) very frequently suffer anemia. Correction of anemia by means of recombinant erythropoietin (rEpo) is possible and useful, but safety and efficacy must be

assessed. METHODS: This multicenter, prospective, open study included patients with a cadaver renal transplant, CAN, and non-ferropenic anemia. The aim of the study was to determine the safety and efficacy of treatment with rEpo to target hematocrit (HCT) values around 35% and/or hemoglobin (Hb) levels of 11 g/dL. RESULTS: Twenty-four patients were included: 71% males and 29% females aged 49.5 +/- 14 years. At last follow-up, 48% did not show anemia-related symptoms, and 19% experienced adverse events possibly or probably related to rEpo. In 86% of cases, anemia was corrected and in 71%, graft survival was conserved. Patients whose anemia was not corrected had poor initial renal function (sCr 5 +/- 1 mg/dL vs sCr 3.2 +/- 1 mg/dL, P = .028). Patients with graft survival showed correction of anemia (P = .001) on a relatively low dose of rEpo and without a significant increase in blood pressure. CONCLUSIONS: All patients who had graft survival and only half of those who lost their graft showed a correction of anemia. The rEpo treatment neither accelerated nor decelerated renal failure. The difference between patients in whom anemia was corrected, or not, did not depend upon the previous level of HCT/Hb, but upon worse renal function. Thus, rEpo in patients with CAN is safe and effective, so administration should be initiated early to avoid adverse events deriving from anemia.

Nampoory MR, Johny KV, al-Hilali N, Seshadri MS, Kanagasabhapathy AS. Erythropoietin deficiency and relative resistance cause anaemia in post-renal transplant recipients with normal renal function. Nephrol Dial Transplant. 1996 Jan;11(1):177-81

BACKGROUND. Following successful renal transplantation, blood erythropoietin (Epo) levels peak in two phases during the first 2-3 months, and blood haemoglobin/haematocrit (HB/Hct) levels are restored to normal in a period of 2-6 months. However, some transplant recipients continue to remain anaemic in spite of normal graft function and in the absence of recognizable causes. The role of endogenous Epo production in the causation of anaemia in such patients is poorly understood and has been investigated in this study. METHODS. Twenty-three post-renal transplant recipients with stable normal renal function were studied. Eleven of these patients had normal HB/Hct levels (group 1) and served as control for the rest 12 patients with anaemia (group 2). Patients included in group 2 had no readily recognizable cause for their anaemia. Other laboratory and clinical findings were similar in both groups. Patients with erythrocytosis were excluded. Serum Epo levels were measured in all patients. Five patients in group 2 were treated with recombinant human erythropoietin (rHuEpo) and their erythropoietic response was assessed. rHuEpo was discontinued when the target Hb/Hct levels (lowest normal range) were achieved and the patients were followed up for a further period of 9-12 months. RESULTS. Five patients in group 1 had normal expected serum Epo levels whereas the other six patients had inappropriately high serum Epo levels with respect to their Hb/Hct status suggestive of relative ¿EPO resistance'. Serum Epo levels in all patients except two in group 2 were low indicative of 'Epo deficiency'. The two exceptional patients in group 2 had higher serum Epo levels in the presence of anaemia suggestive of relative ¿Epo resistance'. All five patients treated with rHUEpo responded adequately by achieving normal Hb/Hct levels. Three of them were originally ¿Epo deficient' and they reached target Hb/Hct levels in a mean period of 4 weeks, requiring a mean cumulative rHuEpo dose of 428.3 units/kg. The other two patients with higher initial serum Epo levels, and considered to be ¿Epo resistant' required an average of 11 weeks of treatment and a mean cumulative rHuEpo dose of 1582.5 units/kg, indicating an increased Epo demand. On cessation of therapy the Hb/Hct levels fell in all five patients to pretreatment values in 6 months. CONCLUSIONS. There are important variations in the endogenous Epo production in renal transplant patients with normal renal function, the cause of which is not clear. Epo deficiency and relative Epo resistance play a causative role for anaemia in some post-renal transplant recipients with stable normal renal function. They respond adequately to rHuEpo administration.

Gleissner CA, Klingenberg R, Staritz P, Koch A, Ehlermann P, Wiggenhauser A, Dengler TJ. Role of erythropoietin in anemia after heart transplantation. Int J Cardiol. 2006 Oct 10;112(3):341-7.

BACKGROUND: Anemia after heart transplantation is common; however, there are scant data on etiology and treatment. This study evaluates type of anemia and the effects of erythropoietin therapy. METHODS: In 37 anemic heart transplant recipients (31 male/59.1+/-10.3 years/hemoglobin <12.0 g/dl), complete anemia work-up was performed including erythropoietin determination. For three months, 12 anemic patients with renal failure (9 male/64.1+/-13.6 years) were treated with 1-3x4000 IU of epoietin beta/week; treatment endpoints were hemoglobin levels and quality of life as determined by questionnaire. RESULTS: In 31 patients no other cause of anemia than renal insufficiency (mean creatinine 1.9+/-0.9 mg/dl, mean calculated GFR 50.8+/-21.5 ml/min, no hemodialysis) was found; in 93.5% of these patients with renal insufficiency, measured erythropoietin levels were markedly lower than predicted [Beguin Y, Clemons GK, Pootrakul P, Fillet G. Quantitative assessment of erythropoiesis and functional classification of anemia based on measurements of serum transferrin receptor and erythropoietin. Blood 1993; 81(4):1067-1076.]. There was an inverse correlation of hemoglobin levels with serum creatinine/creatinine clearance and a strong trend for inverse correlation of erythropoietin levels. All 12 patients treated with erythropoietin showed a significant increase in hemoglobin levels after three months returning to pre-treatment values within 3 months of cessation of therapy (before study 10.8+/-1.1 g/dl, end of study 14.1+/-1.7 g/dl, three months after end of study 11.6+/-2.1 g/dl; p<0.005). Quality of life was significantly improved in eight patients (75%). CONCLUSIONS: Anemia after heart transplantation is associated with moderate renal failure and low erythropoietin levels in most patients. Erythropoietin therapy resulted in increased hemoglobin levels in all and

improved quality of life in 75% of patients. Erythropoietin may be a superior marker of functional renal impairment after heart transplantation; its therapeutic substitution allows effective anemia management and improves quality of life.

Lietz K, Lao M, Paczek L, Górski A, Gaciong Z. The impact of pretransplant erythropoietin therapy on late outcomes of renal transplantation. Ann Transplant. 2003;8(2):17-24.

OBJECTIVES: The introduction of recombinant erythropoietin (rHu-EPO) has been shown to reverse anemia of chronic renal failure and was able to almost completely obviate the need for repeated blood transfusions (BT), the most potent cause of allostimulation in renal transplant candidates. The series describes single center experience of the pretransplant BT and rHu-EPO therapy effects on late outcomes of cadaveric renal transplantation. METHODS: We retrospectively analyzed data of 502 adult recipients of primary renal allograft between 1990-1997 whose graft survived > 6 months. In the study group 51 patients were treated prior to transplantation with de novo rHu-EPO therapy, 207 patients received BT, 184 patients were switched from BT to rHu-EPO therapy, and 60 patients did not require treatment. The groups were compared in respect to pretransplant % PRA, frequency of acute rejections and graft survival. RESULTS: At one-year graft survival was similar between groups, however at five years recipients of de novo rHu-EPO and those who have converted from BT to rHu-EPO experienced only 7% graft loss, as compared to 22% of patients treated with BT, and 18% of patients who did not require treatment, $p < 0.001$. The pretransplant therapy with rHu-EPO was associated with decreased frequency of late episodes of rejection from 0.42 to 0.27, $p = 0.03$. There were no differences between groups in the number of highly sensitized (PRA > 20%) at the time of transplantation. CONCLUSIONS: The use of rHu-EPO as de novo therapy or conversion from BT treatment to rHu-EPO prior to transplantation was associated with a decline in late posttransplant alloreactivity and improved late renal graft survival.

Mohiuddin MK, El-Asir L, Gupta A, Brown A, Torpey N, Ward M, Talbot D, Ahmed S. Perioperative erythropoietin efficacy in renal transplantation. Transplant Proc. 2007 Jan-Feb;39(1):132-4.

BACKGROUND: There is no consensus on the usage of erythropoietin in the immediate postoperative period to prevent anemia and delayed graft function. METHODS: A retrospective case note audit of renal transplants included hemoglobin (Hb) and serum creatinine (Scr) values preoperatively as well as at days 7, 14, 30, 60, and 90. Patients were categorized as those receiving erythropoietin during the first 6 months posttransplant (Epo+ve) and those not receiving any erythropoietin (Epo-ve). RESULTS: Hb decreased from 12.4 +/- 1.6 g/L preoperatively to 9.5 +/- 1.5 g/L at day 14 and then rose to 10.5 +/- 1.6 g/L at 1 month and 12.4 +/- 1.7 g/L at 3 months. There was no difference in absolute Hb values in three transplant groups. Scr decreased from 597.0 +/- 200.1 mmol/L preoperatively to 254.1 +/- 196.9 mmol/L at day 14 and continued to fall to 163.8 +/- 98.9 mmol/L at 1 month and 147.8 +/- 66.9 mmol/L at 3 months. There was no difference in absolute Hb values and delayed graft function in the three transplant groups. CONCLUSION: With respect to anemia and delayed graft function, the use of erythropoietin in the first 3 months had little impact. We suggest that such an expensive medication may be safely omitted in the immediate postoperative period.

Nagarajan S, Mansfield E, Hsieh S, Liu R, Hsieh F, Li L, Salvatierra O Jr, Sarwal MM. Transplant reno-vascular stenoses associated with early erythropoietin use. Clin Transplant. 2007 Sep-Oct;21(5):597-608.

BACKGROUND AND OBJECTIVES: This report describes an unusual presentation of severe hypertension (HTN) in a subset of pediatric kidney recipients treated with a steroid avoidance pediatric renal transplantation protocol. The HTN was secondary to atypical, reno-vascular abnormalities (RVA) of the transplanted vasculature, temporally associated with erythropoietin (EPO) use. DESIGN, SETTING, PARTICIPANTS, AND MEASUREMENTS: To investigate the clinical significance underlying this event, a retrospective clinical study of 100 pediatric renal transplants was undertaken (50 steroid-free and 50 matched steroid-based controls), with peripheral blood transcriptional analysis of four RVA patients and controls. RESULTS: Regardless of a higher observed incidence of anemia ($p < 0.001$) and greater overall EPO usage in the first post-transplant year in steroid-free patients, the incidence of new-onset HTN at one yr was significantly less in the steroid-free cohort ($p = 0.03$). Nevertheless, early EPO (first week post-transplant) was significantly associated with the combinatory findings of new-onset HTN ($p = 0.03$) and RVA ($p = 0.007$). Molecular mechanisms of RVA injury were investigated further by peripheral blood cDNA microarray gene expression profiling. A panel of 42 transcripts differentiated patients with RVA and HTN from three sets of matched controls, with and without HTN and EPO use, with 100% concordance ($p < 0.001$). The biological processes governed by these significant genes suggest a role for EPO regulation of growth factor receptor ubiquitination as a putative mechanism for renal vascular injury. CONCLUSION: This study cautions against the use early post-transplant use of EPO in immunosuppression regimens with steroid minimization/avoidance, which may have an increased incidence of post-transplant anemia.

McDevitt LM, Smith LD, Somerville KT, Corbett JL, Shihab FS. A retrospective assessment of pre-treatment variables on the response to darbepoetin alfa after renal transplantation. Am J Transplant. 2005 Aug;5(8):1948-56.

This retrospective review assesses the efficacy of darbepoetin alfa for treating anemia after renal transplantation. Patients were evaluated over a 12-week period, and efficacy was based on achieving hemoglobin >12 g/dL. Thirty-six patients were analyzed (53% male, 53% cadaveric allografts, median age 42.5 years). Baseline creatinine clearance ranged from approximately 15 to >100 mL/min. Most patients initiated darbepoetin alfa <3 months (50%) or >12 months (44%) after transplantation, 19% were previously receiving recombinant human erythropoietin (rHuEPO), and 47% were on concomitant ACE inhibitors. The majority of patients received either tacrolimus- (53%) or cyclosporine- (44%) based immunosuppression. Overall, 29 (81%) patients achieved the hemoglobin target with a mean time to response of 4.4 weeks. Neither the time to anemia onset, previous rHuEPO therapy, concomitant ACE inhibitor, allograft source, immunosuppressive regimen, nor degree of renal function affected the proportion of patients achieving the hemoglobin target, time to response or darbepoetin alfa dose requirement. Patients with anemia >12 months post-transplantation or on concomitant ACE inhibitors required a significantly longer duration of therapy. No adverse events associated with darbepoetin alfa therapy were detected. These results demonstrate that darbepoetin alfa is a safe and effective treatment for anemia in renal transplant recipients.

Kessler M. Erythropoietin and erythropoiesis in renal transplantation. Nephrol Dial Transplant. 1995;10 Suppl 6:114-6.

This report reviews the features of erythropoietin (Epo) production after renal transplantation. Successful kidney transplantation leads to the correction of renal anaemia over an 8-10 week period. An early ineffective peak of serum Epo may occur when there is delayed graft function. A late peak follows the decrease in serum creatinine and this is associated with a rise in haemoglobin. Serum Epo returns to normal when the haematocrit reaches 32%. Acute early rejection causes a striking reduction in serum Epo and reticulocytosis. In some patients the haematocrit continues to increase after complete correction of anaemia, resulting in post-transplant erythrocytosis (PTE). PTE generally appears to be an idiopathic erythrocytosis independent of Epo secretion. A greater Epo sensitivity of erythroid progenitors has been suggested. Theophylline and angiotensin converting enzyme inhibitors, which attenuate Epo production, can be used to treat PTE. The second part of this report describes the possible impact of human recombinant Epo (rHuEpo) on renal transplantation. The avoidance of blood transfusion with rHuEpo should eliminate the initiation of anti-HLA sensitization in uraemic patients without previous pregnancy and prior allograft. In some but not all presensitized patients transfusion withdrawal may reduce the sensitization level. There is currently no evidence that the reversing of anaemia by rHuEpo in kidney recipients impairs early graft function. Our results suggest that treatment with rHuEpo prior to transplantation may prevent the appearance of PTE. rHuEPO will reverse anaemia in patients with a failing graft and severe anaemia with little risk of accelerating graft failure and adverse events.

Goodnough LT. The role of iron in erythropoiesis in the absence and presence of erythropoietin therapy. Nephrol Dial Transplant. 2002;17 Suppl 5:14-8.

Preoperative autologous blood donation has served as a model for blood loss anaemia. Studies in these patients, along with clinical trials of i.v. iron and recombinant human erythropoietin (rHuEPO) therapy, have furthered our understanding of the relationship between erythropoietin, iron, and erythropoiesis. With supplemental oral iron, the endogenous erythropoietic response to routine autologous blood donation and to the anaemia of chronic illness has been shown to be modest, but predictable. In more aggressive donation and more severe anaemia, the endogenous erythropoietic response is more substantial, but still predictable. Studies in patients undergoing aggressive phlebotomy whilst receiving rHuEPO demonstrate a wide variation in response to rHuEPO dose. This variability is not related to age or gender and suggests factors such as iron-restricted erythropoiesis may be responsible. Supporting evidence arises from the superior erythropoietic response observed in patients with haemochromatosis. These patients maintain very high serum iron and transferrin saturation levels. In response to serial phlebotomy these patients can mount an endogenous erythropoietin response up to five-times greater than healthy individuals. When treated with rHuEPO, patients with haemochromatosis respond with much greater RBC expansion volumes than patients receiving rHuEPO and iron supplementation. Studies show no difference in the degree of endogenously stimulated erythropoiesis between patients with measurable iron stores and those without. However, when treated with rHuEPO, increased erythropoiesis has been observed in patients with measurable iron stores compared with those without. This suggests that, while oral iron supplementation may be sufficient to keep pace with endogenously stimulated erythropoiesis, it may not be adequate to prevent iron-restricted erythropoiesis during rHuEPO therapy. Some studies have suggested that i.v iron may prevent iron-restricted erythropoiesis during rHuEPO therapy although further research is needed. The availability of better tolerated i.v. iron preparations provides an ideal opportunity to study the value of iron therapy in patients with acute blood loss, particularly those undergoing rHuEPO therapy.

- **Anémie lors d'une circulation extra-corporelle (CEC) ou au décours d'une chirurgie cardiaque**

L'utilisation de l'EPO chez les patients anémiés n'a pas d'intérêt lors des chirurgies cardiaques, notamment en cas de circulation extra-corporelle (CEC) ou en post-chirurgie cardiaque :
- chez les patients jeunes : il est recommandé de ne pas corriger l'anémie ;
- chez les patients âgés : il est recommandé de transfuser.

De plus, chez les porteurs de valves, l'EPO peut avoir des effets indésirables ; de même, en cas de pontage (risque de thrombose).

A la phase initiale, il est difficile d'évaluer l'effet de l'EPO : les études ne peuvent pas être réalisées en raison des nombreuses complications liées à la pathologie sous-jacente.
A distance, l'anémie observée est le plus souvent secondaire aux traitements associés.

Par ailleurs, des études randomisées en double-aveugle (Madi-Jebaa 2004, Palazzuoli 2006 et Karkouti 2006) ne montrent pas d'augmentation significative de la concentration d'hémoglobine ni de diminution des besoins en transfusion.

Il n'y a donc pas d'intérêt à prescrire des EPO pour traiter les anémies des patients lors d'une CEC ou au décours d'une chrirurgie cardiaque.

Effet de l'EPO chez les patients anémiés lors d'une chirurgie cardiaque

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Madi-Jebaa (2004)	**Randomisée double-aveugle versus placebo** **N = 120** patients post- chirurgie cardiaque dont [Hb] entre 7 et 10 g/dl	3 Groupes : **Gpe 1** : contrôles **Gpe 2** : Fer IV postop + IHSC **Gpe 3** : Fer IV + dose unique d'EPO 300 UI/kg postop	30 j post chirurgie	J1, J5, J15, J30 . Besoin en transfusion . [Hb] . Nombre de réticulocytes .Taux de ferritine sérique	Comparaison des 3 groupes : . Besoin en transfusion : **NS** . Nombre de réticulocytes **-** à J5 : ↑ **S p = 0.007 (gpe II et III)** - à J15 : ↓ rapide dans les 3 groupes **NS** . Taux de ferritine : ↑ **S p < 0.001** (gpe II et gpe III) . [Hb] : ↑ **NS** dans les 3 groupes
Karkouti (2006)	**Randomisée double-aveugle Versus placebo :** **N = 38** mais seulement 31/38 évaluables ont un taux d'hb entre 7 et 9 g/dL J7 post-op cardiaque ou orthopédique	**3 groupes :** **Gpe 1** : contrôle : n = 10 **Gpe 2** : fer IV seul : 200mg J1, J2, J3 postop : n = 11 **Gpe 3** : Fer IV 200mg + rHuEPO 600 UI/kg J1 et J3 : n = 10 J1 : 300 UI/kg IV + 300 UI/kg sc J3 : 600 UI/kg sc Certains patients ont été transfusés après la randomisation	6 sem	- [Hb] de J1 à J7 - Nombre de réticulocytes - ↑ de l'Hb - [Hb]	- J1-J7 : [Hb] : ↓: 31/38 : 8.4 g/dL - à J7 : **.** [Hb] : ↑ **NS** Gpe 1 : ↑ 0.7 g/dL Gpe 2 : ↑ 0.9g/dL . groupe 3 : nombre + élevé de réticulocytes Gpe 3 : ↑ 1 g/dL **-** A S6 : ↑ [Hb] : **NS** Gpe 1 : ↑ 3.7 g/dL Gpe 2 : ↑ 4 g/dL Gpe 3 : ↑ 4.5 g/dL Résultats similaires pour les patients transfuses et non transfusés
Mocini 2008	**Ouverte** **N = 67 patients avant chirurgie cardiaque dont 40**	EPO : Epoétine alfa : 40000 UI		EPO endogène (eEPO) Troponine I CK-MB	eEPO mesurée avant chirurgie non corrélée aux taux de troponine I et aux pics de CK-MB en postchirurgie

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
	patients randomisés : . n = 20 ont reçu un traitement standard . n = 20 ont reçu EPO + traitement standard				Patients traités par EPO versus contrôles : Troponine I : **NS** Pics de CK-MB : **NS**
Ootaki (2007)	**Ouverte : N = 82 enfants** avant chirurgie cardiaque	Groupe E0 : n = 20 Aucun traitement Avant l'opération pdt 7j : Groupe E2 : n = 27 rHuEPO 200 UI/kg+ Fer 2mg/kg Groupe E4 : n = 35 rHuEPO : 400 UI/kg + fer 4 mg/kg		Paramètres hématologiques Fer Nombre de transfusion de CGR	Nbre de transfusion GR : **NS** E0 : 40% E2 : 14.8 % E4 : 22.9% [Hte] : ↑ EO : 0.7 % E2 : 1.3% E4 : 1.9%
Locatelli (1994)	**N= 2 enfants** Age : 6 et 7 ans [Hb]=7.1 & 7.5 g/dL - transplantation cardiaque sous cyclosporine A	EPO sc : 75 U/kg 3x /sem. pdt 1 M puis 2x /sem.	2 M	- [Hb] - Nombre de réticulocytes - Nbre de CGR - Tolérance	Restauration de l'érythropoïèse : - nbre de réticulocytes : ↑ de 156 à 172 10^9/L - [Hb] : ↑ de 7.1 à 9.1 g/dL après 15 j de trt et plus de 11 g/dL après 1 M de trt. - 0 CGR - Bonne tolérance - Prise alimentaire : **≠ NS**
Ferraris (2007)	Guidelines	Identifier les personnes à risques: - âge avancé - volume de sang faible avant l'opération (anémie ou petite taille) - prise de médicaments antithrombotiques en préopératoire ou antiplaquettaires - réopération - opérations d'urgence - comorbidités non cardiaques Prendre des mesures pour limiter la perte de sang en peropératoire et post-opératoire : - médicaments augmentant le volume sanguin en préopératoire : EPO - médicaments diminuant les saignements en postopératoire : antifibrinolytiques - conseils pour conserver le sang - transfusion de sang autologue permet de conserver le sang du patient en préopératoire			

CK-MB: creatine-kinase isoenzyme GR : globules rouges
IHSC : complexe d'hydroxyde de sucrose ferrique NYHA : New-York Heart Association
CGR : concentré de globules rouges

Bibliographie

Les référentiels de la Juste prescription du CEDIT (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 1994.

1. Madi-Jebara SN, Sleilaty GS, Achouh PE, Yazigi AG, Haddad FA, Hayek GM, Antakly MC, Jebara VA. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. J Cardiothorac Vasc Anesth. 2004 Feb;18(1):59-63
3. Karkouti K, McCluskey SA, Ghannam M, Salpeter MJ, Quirt I, Yau TM.Intravenous iron and recombinant erythropoietin for the treatment of postoperative anemia. Can J Anaesth. 2006 Jan;53(1):11-9

4. Mocini D, Muso P, Guendouz E, De Marco L, Mele L, Cini R, Sordini P, Alois A, Costantino A, Arima S, Gentili C, Santini M. Endogenous erythropoietin and a single bolus of 40,000 IU of epoetin alpha do not protect the heart from ischaemia-reperfusion injury during extracorporeal circulation for cardiac surgery. Perfusion. 2008 May; 23(3):187-92.
5. Ootaki Y, Yamaguchi M, Yoshimura N, Oka S, Yoshida M, Hasegawa T. The efficacy of preoperative administration of a single dose of recombinant human erythropoietin in pediatric cardiac surgery. Heart Surg Forum. 2007;10(2):E115-9.
6. Locatelli F, Zecca M, Mamprin F, Gamba A, Giorgiani G, De Stefano P. Recombinant human erythropoietin may correct erythropoietin-deficient hyporegenerative anaemia in children given cardiac transplantation. Br J Haematol. 1994 Nov;88(3):6235.
7. Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Royston BD, Bridges CR, Higgins RS, Despotis G, Brown JR; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, Body S. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline.
Society of Thoracic Surgeons Blood Conservation Guideline Task Force. Ann Thorac Surg. 2007 May; 83(5 Suppl):S27-86.

Résumés-abstracts

Madi-Jebara SN, Sleilaty GS, Achouh PE, Yazigi AG, Haddad FA, Hayek GM, Antakly MC, Jebara VA. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. J Cardiothorac Vasc Anesth. 2004 Feb;18(1):59-63

OBJECTIVES: The aim of this study was to examine whether intravenous iron III-hydroxide sucrose complex (IHSC) used alone was sufficient to provide rapid correction of anemia after cardiac surgery and whether additional stimulation of erythropoiesis is possible by means of a single low dose of recombinant-human erythropoietin (r-HuEPO) administration. DESIGN: Prospective, randomized, double-blind study. SETTING: The study was conducted in a university hospital. PARTICIPANTS: One hundred twenty American Society of Anesthesiologists II or III patients, who underwent elective cardiac surgery using cardiopulmonary bypass and in whom postpump hemoglobin ranged between 7 and 10 g/dL. INTERVENTIONS: Patients were divided into 3 groups: group I = control; group II received postoperative intravenous iron supplementation with an iron III-hydroxide sucrose complex (IHSC); and group III received IV iron and a single dose of r-HuEPO (300 U/kg). MEASUREMENTS AND RESULTS: No significant difference in transfusion needs was observed among the 3 groups (22%, 25%, and 17% of patients transfused in groups I, II, and III, respectively). Hemoglobin levels, reticulocyte counts, and serum ferritin levels were evaluated at different time intervals (until day 30 postoperatively). No side effects because of iron administration were noted in the study. Reticulocyte counts increased rapidly at day 5 (2.24% +/- 1.11%, 1.99% +/- 1.44%, and 3.84% +/- 2.02% in groups I, II, and III, respectively) and decreased after day 15 in the 3 groups. Ferritin levels increased significantly at day 5 in the 2 treated groups (899.33 +/- 321.55 ng/mL in group II, 845.75 +/- 289.96 ng/mL in group III v 463.15 +/- 227.74 ng/mL in group I). In group I, ferritin levels, after a slight elevation on day 5, decreased at day 15 to lower than baseline levels. No significant difference in hemoglobin increase was noted among the 3 groups. CONCLUSION: Postoperative intravenous iron supplementation alone or in combination with a single dose of r-HuEPO (300 U/kg) is not effective in correcting anemia after cardiac surgery.

Karkouti K, McCluskey SA, Ghannam M, Salpeter MJ, Quirt I, Yau TM.Intravenous iron and recombinant erythropoietin for the treatment of postoperative anemia. Can J Anaesth. 2006 Jan;53(1):11-9

PURPOSE: To determine if early recovery from severe post-operative anemia is accelerated by iv iron therapy alone or in combination with recombinant erythropoietin (EPO). METHODS: In this double-blinded, placebo-controlled randomized study, consenting adult patients without preoperative anemia whose hemoglobin concentration (Hb) was 70 to 90 g x L(-1) on the first day after cardiac or orthopedic surgery (POD 1) were assigned to one of three groups: control, iv iron alone (200 mg of iron sucrose on POD 1, 2, and 3) or in combination with EPO (600 U x kg(-1) on POD 1 and 3). The primary outcome was increase in Hb (adjusted for red blood cell transfusions) from POD 1 to 7. Analysis was by intention-to-treat in patients for whom the primary outcome was available. Group effect was analyzed by the ANOVA test, and between-group differences were specified with a Duncan multiple-range test. RESULTS: The primary outcome was available in 31 of 38 randomized patients. The average POD 1 Hb was 84 +/- 4 g x L(-1). There were no between-group differences in outcomes except for higher reticulocyte counts on POD-7 in the combination group. The average adjusted one-week increases in Hb were 7 +/- 8 g x L(-1) in the control group (n = 10), 9 +/- 9 g x L(-1) in the iv iron group (n = 11), and 10 +/- 14 g x L(-1) in the combination group (n = 10). The average adjusted six-week increases in Hb were 37 +/- 14 g x L(-1) in the control group, 40 +/- 7 g x L(-1) in the iv iron group, and 45 +/- 12 g x L(-1) in the combination group. CONCLUSION: Early postoperative treatment with iv iron alone or in combination with EPO does not appear to accelerate early recovery from postoperative anemia.

Mocini D, Muso P, Guendouz E, De Marco L, Mele L, Cini R, Sordini P, Alois A, Costantino A, Arima S, Gentili C, Santini M. Endogenous erythropoietin and a single bolus of 40,000 IU of epoetin alpha do not protect the heart from ischaemia-reperfusion injury during extracorporeal circulation for cardiac surgery. Perfusion.2008 May; 23(3):187-92.

Erythropoietin (EPO) exerts a tissue-protective activity in several non-haematopoietic tissues such as heart, brain, spinal cord and muscle. We evaluated the relationship between pre-operative endogenous EPO blood levels and myocardial damage in patients undergoing cardiopulmonary bypass (CPB). Furthermore, we investigated whether pre-operative administration of a single bolus of 40,000 IU epoetin alpha (EPOalpha) would reduce troponin I or creatine kinase isoenzyme (CK-MB) after on-pump coronary artery bypass graft (CABG) surgery. Sixty-seven patients (45 CABG, 22 valvular surgery) were enrolled. EPO was measured in the pre-surgical period and correlated to post-surgical troponin I and CK-MB peaks. Subsequently, forty patients scheduled for CABG were randomized into two groups, receiving, respectively, a) standard medical and surgical treatment (20 patients) and b) the same treatment plus 40,000 IU of EPOalpha in a single bolus injection in the immediate pre-surgical period (20 patients). In our population, we did not find any correlation between pre-surgical EPO and post-surgical troponin I or CK-MB peaks (p Pearson > 0.05). Furthermore, patients treated with EPOalpha did not show differences compared to the control group in either troponin I (1.7+/-1.8 vs 2.6+/-3.4, p>0.05) or CK-MB (19.6 +/-13.2 vs 17.1+/-12.6, p>0.05) peaks measured in the post-surgical period.

Ootaki Y, Yamaguchi M, Yoshimura N, Oka S, Yoshida M, Hasegawa T. The efficacy of preoperative administration of a single dose of recombinant human erythropoietin in pediatric cardiac surgery. Heart Surg Forum. 2007;10(2):E115-9.

BACKGROUND: Preoperative autologous blood donation with recombinant human erythropoietin (rHuEPO) is effective in adults. However, there are problems concerning the blood access, cost, and blood storage in children. The purpose of this study was to evaluate the efficacy of administering a single dose of rHuEPO without blood donation in children undergoing pediatric cardiac surgery. METHODS: Eighty-two children (72 with noncyanotic heart disease, and 10 with cyanotic heart disease) whose hematocrit values were less than 45% were included in this prospective, nonrandomized study. The children were divided into 3 groups: group E0 (n = 20) was not treated with rHuEPO and iron sulfate; group E2 (n = 27) was treated with 200 IU/kg of rHuEPO and 2 mg/kg of iron sulfate; and group E4 (n = 35) was treated with 400 IU/kg of rHuEPO and 4 mg/kg of iron sulfate. Administration of rHuEPO was performed subcutaneously 7 days before the operation. The hematological and iron parameters were measured perioperatively. RESULTS: A lower proportion of children treated with rHuEPO (group E2, 14.8%; group E4, 22.9%) than children without rHuEPO (group E0, 40.0%) were exposed to RBC transfusions; however, there was no significance. The elevations of the hematocrit levels were 0.7% in group E0, 1.3% in group E2, and 1.9% in group E4. The elevation of the hematocrit was greater in patients with anemia (hematocrit < or =37%). CONCLUSIONS: Although the effectiveness for avoiding transfusion was not clear, the administration of a single dose of rHuEPO without autologous blood donations had an effect by increasing hematocrit levels.

Locatelli F, Zecca M, Mamprin F, Gamba A, Giorgiani G, De Stefano P. Recombinant human erythropoietin may correct erythropoietin-deficient hyporegenerative anaemia in children given cardiac transplantation. Br J Haematol. 1994 Nov;88(3):623-5.

Cyclosporin-A reduces erythropoietin production and, together with the inhibitory effect of cytokines on erythropoiesis, may be potentially responsible for the anaemia observed in some patients after heart transplantation. Two children given cardiac transplantation and receiving cyclosporin-A developed transfusion-dependent hyporegenerative anaemia. Erythropoietin production was inappropriately low for the degree of anaemia, with an observed/predicted log (serum EPO) ratio of 0.54 and 0.49, respectively. The children were treated with rHuEPO at a dose of 75 U/kg three times weekly for 1 month and then twice weekly via subcutaneous injection. No further transfusion was necessary and restoration of normal erythroid activity was obtained, with normal haemoglobin values. No adverse effects were observed. Our experience suggests that recombinant human erythropoietin may be useful in treating the anaemia associated with cardiac transplantation.

Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Royston BD, Bridges CR, Higgins RS, Despotis G, Brown JR; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, Body S. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline.
Society of Thoracic Surgeons Blood Conservation Guideline Task Force. Ann Thorac Surg. 2007 May; 83(5 Suppl):S27-86.

BACKGROUND: A minority of patients having cardiac procedures (15% to 20%) consume more than 80% of the blood products transfused at operation. Blood must be viewed as a scarce resource that carries risks and benefits. A careful review of available evidence can provide guidelines to allocate this valuable resource and improve patient outcomes. METHODS: We reviewed all available published evidence related to blood

conservation during cardiac operations, including randomized controlled trials, published observational information, and case reports. Conventional methods identified the level of evidence available for each of the blood conservation interventions. After considering the level of evidence, recommendations were made regarding each intervention using the American Heart Association/American College of Cardiology classification scheme. RESULTS: Review of published reports identified a high-risk profile associated with increased postoperative blood transfusion. Six variables stand out as important indicators of risk: (1) advanced age, (2) low preoperative red blood cell volume (preoperative anemia or small body size), (3) preoperative antiplatelet or antithrombotic drugs, (4) reoperative or complex procedures, (5) emergency operations, and (6) noncardiac patient comorbidities. Careful review revealed preoperative and perioperative interventions that are likely to reduce bleeding and postoperative blood transfusion. Preoperative interventions that are likely to reduce blood transfusion include identification of high-risk patients who should receive all available preoperative and perioperative blood conservation interventions and limitation of antithrombotic drugs. Perioperative blood conservation interventions include use of antifibrinolytic drugs, selective use of off-pump coronary artery bypass graft surgery, routine use of a cell-saving device, and implementation of appropriate transfusion indications. An important intervention is application of a multimodality blood conservation program that is institution based, accepted by all health care providers, and that involves well thought out transfusion algorithms to guide transfusion decisions. CONCLUSIONS: Based on available evidence, institution-specific protocols should screen for high-risk patients, as blood conservation interventions are likely to be most productive for this high-risk subset. Available evidence-based blood conservation techniques include (1) drugs that increase preoperative blood volume (eg, erythropoietin) or decrease postoperative bleeding (eg, antifibrinolytics), (2) devices that conserve blood (eg, intraoperative blood salvage and blood sparing interventions), (3) interventions that protect the patient's own blood from the stress of operation (eg, autologous predonation and normovolemic hemodilution), (4) consensus, institution-specific blood transfusion algorithms supplemented with point-of-care testing, and most importantly, (5) a multimodality approach to blood conservation combining all of the above.

- **Traitement des anémies du post-partum**

L'anémie du post-partum est une anémie transitoire aiguë.

L'étude de Meyer 1995 randomisée double-aveugle versus placebo n'a pas montré d'augmentation des réticulocytes, de la concentration en hémoglobine et de l'hématocrite ni de diminution du nombre de transfusion sanguine notamment sur le long terme.
Seules les études comparatives ouvertes de plus faible effectif montrent parfois une augmentation des réticulocytes, de l'hématocrite et de la concentration en hémoglobine mais ces variations ne sont pas constantes.
Par ailleurs, il existe des alternatives thérapeutiques : le Fer IV ou per os et dans le cas échéant, des transfusions sont envisageables.

Il n'est donc pas recommandé d'utiliser des EPO pour traiter les anémies du post-partum.

Résumé tabulé des effets de l'EPO dans les anémies du post partum

Auteur	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Meyer (1995)	**Randomisée Prospective double-aveugle multicentrique vs placebo N = 345** EPO : n=35 Pla : n=36 [Hb] normal : n=274	Epoétine alfa IV 10 000 UI 2x à 24h d'intervalle Pla	5 J	- [Hb] - [Hte]	- [Hb] à J5 : ↑ **NS** EPO : de [7.4 - 9.9] à [6.9 -12.6] en g/dL **P< 0001** Pla : de [6.2 - 9.9] à [6.6 -12.1] - [Hte] à J5 : ↑ **NS** EPO : de [21 - 34] à [21 - 38] en g/dL Pla : de [19 - 31] à [20 - 37]
Zimmermann (1994)	**Randomisée prospective, comparative N = 95** [Hb] < 10 g/dl	Epoétine alfa sc **Gpe A : n = 26** 150 UI/kg/j sc pdt 2 j **Gpe B : n = 25** 150 UI/kg/j IV pdt 2 j **Gpe C : n = 22** 300 U/kg/j sc pdt 1 j **Gpe D : n = 22** 300 UI/Kg/j IV pdt 1 j	42 j	[Hb], [Hte], Nbre de réticulocytes	A J14 et J42: - [Hb], [Hte] et le nbre de GR : **≠ NS** . [Hb] g/dL: Gpe A : de 8.8 à 12.6 Gpe B : de 9.2 à 12.7 Gpe C : de 8.7 à 12.8 Gpe D : de 8.5 à 12.5 . [Hte] : Gpe A : de 27 à 38% Gpe B : de 27 à 39% Gpe C : de 26 à 38% Gpe D : de 26 à 38% A J4 : ↑ des erythrocytes puis taux normal J42 : ↓**S** du stock de fer dans les 4 gpe La dose de 300 UI/kg en IV et sc su est aussi efficace que 2 doses de UI/kg en IV et sc sur 2 j.
Breymann (1996)	**Randomisée prospective, comparative** **N = 90** patientes anémiées en postpartum [Hb] < 10 g/dL	Epoétine alfa sc **Gpe 1**: (n=30) : Fer IV + fer PO + Ac Folique **Gpe 2** (n=30) 300UI/kg/j en sc + fer IV + Fer PO + Ac Folique **Gpe 3** (n=30)	6 sem	[Hb], [Hte], Nbre de et réticulocytes	A J 4 et J14 - [Hb] Gpe 3 : ↑ **S** (versus gpe 1 et gpe 2) che les patients ayant eEPO < 145 mU/ml (n 36) Gpe 2 : ↑ **NS** (versus gpe 1) A J4 : - Nbre de réticulocytes versus gpe 1

		300UI/kg/j en IV + Fer PO + Ac Folique			Gpe 2 : ↑ **S** Gpe 3 : ↑ **NS**
Hatzis (2003)	**Prospective comparative contrôlée** **N = 74** [Hb]<11g/dL	Epoétine alfa IV 20 000 UI juste après l'accouchement : n = 37 Fer PO : 80 mg/j pdt 40j post-partum: n = 37	40 j	A J4 et J40 - [Hb], - Nbre de CGR	- A J4 et J40 : Gpe EPO versus gpe contrôle : [Hb] ↑ **S (p = 0.01 (J4) et p = 0.005 à (J4** - Transfusion : . Gpe EPO : n = 0 . Contrôle: n = 6 - Bonne tolérance
Zimmerman n (1995)	**Etudes Ouvertes Contrôlées** **. Etude pilote :** **N=10** [Hb]<8 g/dL **.Etude 1** **Randomisée contrôlée** **N=74** [Hb]<10 g/dL **. Etude 2 :** **N = 95** (Zimmermann 94) **. Etude 3 :** **N = 90** (Breymann 1996)	<u>Etude pilote</u> : n = 5 Epoétine alfa 60 IU/kg IV le 1er j puis sc pdt 4j + fer PO : 80 mg 2x/j Gpe contrôle : fer 80 mg 2x /j <u>Etude 1</u> : Epoétine alfa : Epoétine alfa 60 IU/kg IV le 1er j puis sc pdt 4j + fer PO : 80 mg 2x/j Gpe contrôle : fer 80 mg 2x /j cf étude Cf étude	14j 42 j	- [Hb] et - Nbre de réticulocytes	<u>Etude pilote</u> : - [Hb] : ↑ **S** (A J14) - <u>Etude 1</u> : [Hb] : ↑ **S** (p < 0.05) Nbre de réticulocytes : ↑ **S** (p< 0.01) - <u>Etude 2</u> : A J14 : [Hb] : **NS** entre les groupes Cf étude
Huch (1992)	**Etude randomisée Contrôlée** **N = 74** [Hb] < 10g/dl	Epoétine alfa 4000 UI IV le 1er j et sc pdt 4 j	42 j	A J5, J14, J42 [Hb], [Hte], Nbre de réticulocytes Plaquettes	. A J5, J14, J42 [Hb] : ↑ **S (p < 0.05)** [Hte] **≠ NS** Plq : **≠ NS** Bonne tolérance
Breymann (2000)	**Etude prospective randomisée comparative contrôlée** **N = 60** [Hb] < 10g/dL	**Gpe 1 :** Epoétine alfa IV 300 UI/kg/j pdt 4j + Fer IV **Gpe 2** : Pla + Fer IV pdt 4j **Gpe 3 :** Fer PO +Ac. folique pdt 4j	14 j	A J4, J7, J 14 après le début du traitement (instauré 48-72h postpartum) - [Hte] - Nbre de réticulocytes	A J7 et J14 gpe 1 versus gpe 2 et gpe3 - Nbre de réticulocytes (: ↑ **S** (à J4 versu Fer PO p<0.05 et à J7 : p< 0.01 versus Fer PO Fer IV) - [Hte] : ↑ **S** dans les 3 gpes Tolérance similaire
Makrydimas (1998)	**Etude randomisée, ouverte, Contrôlée** **N = 40** [Hb]<10g/dl 15 jours suivant le post-partum	Epoétine sc: 200UI/kg/j + Fer PO + Ac folique pdt 40 j	40j post-partum	A J1, J3, J5, J10, J15 et J40 psotpartum Nbre de réticulocytes, [Hb], [Hte] et nbre CGR transfusés	. Nbre de réticulocytes à J3 et J 15: ↑ **S (p< 0.05)** . [Hb] ↑ **S** à J5 : ↑ de 2g/dL versus 0.7g/dL **(p< 0.05)** . [Hte] ↑ **S** à J5 **(p< 0.05)** . Nbre de CGR transfusés: Gpe EPO : n = 0 Gpe contrôle : n = 2

					- Nbre de j d'hosp : **S (p<0.005) :** Gpe EPO : 11 jours Gpe contrôle : 14 jours - Allaitement possible : **S (p<0.01):** Gpe EPO : n = 19 Gpe contrôle : n = 10 Bonne tolérance

CGR : concentrés de globules rouges
eEPO : EPO endogène
[Hb] : concentration d'hémoglobine
Plq : plaquettes

Bibliographie :

Les référentiels de la Juste prescription du CEDIT (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 1992.

1. Meyer JW, Eichhorn KH, Vetter K, Christen S, Schleusner E, Klos A, Huch A, Huch R. Does recombinant human erythropoietin not only treat anemia but reduce postpartum (emotional) distress as well ? J Perinat Med. 1995;23(1-2):99-109.
2. Zimmermann R, Breymann C, Huch R, Huch A. rHuEPO in the treatment of postpartum anemia: subcutaneous versus intravenous administration. Clin Investig. 1994;72(6 Suppl):S25-303. Breymann C, Zimmermann R, Huch R, Huch A. Use of recombinant human erythropoietin in combination with parenteral iron in the treatment of postpartum anemia. Eur J Clin Invest. 1996 Feb;26(2):123-30
4. Hatzis T, Cardamakis E, Tsapanos V, Kourounis G, Linardos N, Mantouvalos H, Tzingounis V The effects of recombinant human erythropoietin given immediately after delivery to women with anemia. Curr Med Res Opin. 2003;19(4):346-9.
5. Zimmermann R, Breymann C, Richter C, Huch R, Huch A. rhEPO treatment of postpartum anemia. J Perinat Med. 1995;23(1-2):111-7.
6. Huch A, Eichhorn KH, Danko J, Lauener PA, Huch R. Recombinant human erythropoietin in the treatment of postpartum anemia. Obstet Gynecol. 1992 Jul;80(1):127-31
7. Breymann C, Richter C, Huttner C, Huch R, Huch A Effectiveness of recombinant erythropoietin and iron sucrose vs.iron therapy only, in patients with postpartum anemia and blunted erythropoiesis. Eur J Clin Invest. 2000 Feb;30(2):154-61
8. Makrydimas G, Lolis D, Lialios G, Tsiara S, Georgiou I, Bourantas KL. Recombinant human erythropoietin treatment of postpartum anemia. Preliminary results. Eur J Obstet Gynecol Reprod Biol. 1998 Oct;81(1):27-31

Résumés-abstracts

Meyer JW, Eichhorn KH, Vetter K, Christen S, Schleusner E, Klos A, Huch A, Huch R. Does recombinant human erythropoietin not only treat anemia but reduce postpartum (emotional) distress as well ? J Perinat Med. 1995;23(1-2):99-109.

Based on the established rhEPO treatment of anemia in endstage renal failure, which results in improved quality of life, and on the clinical observation that patients with postpartum anemia treated with rhEPO seemed to gain a more stable mood, we inferred that there is a beneficial side-effect of rhEPO on postpartum blues. The aim of this study was to test the hypotheses 1) that postpartum anemia aggravates, and 2) that treatment of postpartum anemia with rhEPO reduces maternity blues. The results show that on the fifth day postpartum anemic patients score consistently worse than nonanemic women on the Symptom Checklist SCL-90-R, indicating more symptoms and distress in general, and also more symptoms characteristic of maternity blues ($p < 0.05$). On a "Blues Questionnaire," postpartum anemia expresses itself with a reduced "well-being" ($p < 0.001$). Thus, our first hypothesis was verified. There were no differences by the fifth day postpartum between anemic patients receiving either rhEPO or placebo. Our second hypothesis was thus not confirmed within this limited time. We conclude as clinicians that postpartum anemia should be treated effectively to reduce distress and hence the risk for postpartum affective disorders. Follow-up studies after rhEPO treatment beyond the first week post partum are needed. In addition, in investigations on postpartum affective disorders, the hemoglobin concentration should be considered.

Zimmermann R, Breymann C, Huch R, Huch A. rHuEPO in the treatment of postpartum anemia: subcutaneous versus intravenous administration. Clin Investig. 1994;72(6 Suppl):S25-30

The aim of this study was to determine whether single-shot therapy with recombinant human erythropoietin (rHuEPO) is as effective as divided dosing in postpartum anemia for both subcutaneous and intravenous administration. In a randomized prospective study we treated 95 women with postpartum anemia (Hb < 10 g/dl) within 72 h after delivery with rHuEPO (total dose 300 U/kg body weight) and oral iron supplementation in four treatment groups: group A rHuEPO 150 U/kg s.c. once daily for two consecutive days; group B rHuEPO 150 U/kg i.v. once daily for two consecutive days; group C rHuEPO 300 U/kg s.c. once only; group D rHuEPO 300 U/kg i.v. once only. No significant intergroup differences were found in the mean increase of hemoglobin (P = 0.93 for a difference of 1 g/dl). The mean increase in the single-shot groups was 3 g/dl in 14 days. There was a significant reduction of iron stores in all groups. We conclude that single-shot rHuEPO 300 U/kg body weight corrects anemia just as effectively as divided doses on both intravenous and subcutaneous administration. The overall increase in Hb is only slight but preliminary results indicate that the effect can be enhanced by administrating iron intravenously and by an interval therapy with high-dose rHuEPO.

Breymann C, Zimmermann R, Huch R, Huch A. Use of recombinant human erythropoietin in combination with parenteral iron in the treatment of postpartum anemia. Eur J Clin Invest. 1996 Feb;26(2):123-30

The authors compared the effect of recombinant human erythropoietin (rhEPO) in combination with iron with that of iron therapy only in the treatment of postpartum anaemia. Ninety patients (30 patients/group) received either rhEPO (300 U kg-1, i.v. or s.c., once) and iron (parenteral and oral), or iron therapy only. Erythropoiesis was assessed by haemoglobin and haematocrit increase, absolute reticulocyte counting and reticulocyte flow cytometry. Ferrokinetics was assessed by serum ferritin, transferrin and transferrin saturation measurements. There was no difference before therapy for baseline haematological values or iron status. Patients with endogenous EPO levels below 145 mU mL-1 had a significant benefit from intravenous rhEPO administration with highest haematocrit and haemoglobin levels 4 and 14 days after therapy. rhEPO-treated groups showed a higher absolute reticulocyte count 1 and 4 days after therapy and an elevated percentage of high fluorescent reticulocytes (HFRs). Parenteral iron therapy caused a significant increase of ferritin and transferrin saturation, while transferrin concentration decreased. Ferritin and transferrin levels were lowest after i.v. administration of rhEPO, 1 and 4 days after therapy. C-reactive protein concentration was highest in patients who underwent caesarean section until the end of the observation period. A single dose of rhEPO in combination with iron was more effective in treating postpartum anaemia than iron therapy only, in patients who had low EPO levels despite peripartal blood loss. Postpartum low endogenous EPO levels might be a consequence of inhibiting inflammatory cytokines that are released after spontaneous or operative deliveries.

Hatzis T, Cardamakis E, Tsapanos V, Kourounis G, Linardos N, Mantouvalos H, Tzingounis V The effects of recombinant human erythropoietin given immediately after delivery to women with anemia. Curr Med Res Opin. 2003;19(4):346-9.

OBJECTIVE: Anaemia is a common problem during pregnancy and the puerperium. This study was designed to determine the efficacy and safety of giving recombinant human erythropoietin (EPO) to anaemic women during the puerperium. METHOD: Thirty-seven women received a single dose of EPO (20 000 IU intravenously) immediately after delivery. A control population (n = 37) matched according to age and haemoglobin concentration was evaluated. All women received oral iron supplementation for 40 days after delivery. Haemoglobin concentrations were measured 4 and 40 days after delivery. Blood transfusions were given depending on clinical condition and haemoglobin level. RESULTS: Patients treated with EPO had a significantly higher mean haemoglobin concentration than control patients at days 4 and 40. No women in the EPO group required a transfusion, compared with six in the control group. No side-effects and fewer anaemia-related symptoms were observed during EPO treatment. CONCLUSION: EPO given at delivery is effective in decreasing the need for blood transfusion and the incidence of problems associated with anaemia during the puerperium.

Zimmermann R, Breymann C, Richter C, Huch R, Huch A. rhEPO treatment of postpartum anemia. J Perinat Med. 1995;23(1-2):111-7.

Postpartum hemorrhage is a continuing problem occurring in 5-10% of all deliveries. Due to recent problems with blood transfusion, heterologous blood is nowadays restricted to life-threatening indications. As a consequence the clinician is faced with many patients suffering from overt symptoms of anemia. We therefore investigated the effect of recombinant human erythropoietin (rhEPO) in combination with adequate iron supplementation as an alternative for blood transfusion in postpartum anemia. In a pilot study we could show that rhEPO can enhance the effect of endogenous erythropoietin on erythropoiesis. These data could be confirmed in a larger randomized trial. In another study we could show that rhEPO given s.c. is as effective as i.v. Measurement of the iron stores, however, demonstrated low values at the end of pregnancy indicating that iron is a limiting factor for erythropoiesis in postpartum anemia. In a next study i.v. iron combined with rhEPO showed a greater increase in Hb compared to i.v. iron alone. The chosen dose of i.v. iron, however, was too small as shown by the low ferritin levels. We concluded from these previous studies that rhEPO enhances endogenous erythropoiesis, but so far

the effect was only slight (ca 1 g/dl within 14 days); all treated patients developed overt iron deficiency in terms of low ferritin levels despite oral and i.v. iron supplementation; no major side-effects were seen. A further study in healthy non pregnant volunteers demonstrated an effect on erythropoiesis lasting for 3-4 days after a single dose of 300 U/kg rhEPO.

Huch A, Eichhorn KH, Danko J, Lauener PA, Huch R. Recombinant human erythropoietin in the treatment of postpartum anemia. Obstet Gynecol. 1992 Jul;80(1):127-31

Postpartum maternal anemia (hemoglobin concentration below 10 g/dL) is a common problem in obstetrics. Human recombinant erythropoietin, which has been shown to correct the anemia of end-stage renal disease and eliminate the need for transfusions, was used in a comparative study of women with postpartum hemoglobin concentrations below 10 g/dL. Five daily doses of 4000 IU were given. Hematologic and clinical data were compared on days 5, 14, and 42 after therapy in the treated women and in untreated women. Both groups received the same iron and folic acid supplements. Significantly greater increases in reticulocytes, hemoglobin, and hematocrit were seen by day 5 for the treated subjects compared with controls. Ferritin levels were significantly lower in the therapy group than in controls. No differences were seen between the groups in the platelet counts or clinical characteristics. No negative side effects were observed. As in other studies in populations without renal disease, recombinant human erythropoietin enhanced endogenous erythropoiesis over and above the normal physiologic recovery rate.

Breymann C, Richter C, Huttner C, Huch R, Huch A Effectiveness of recombinant erythropoietin and iron sucrose vs.iron therapy only, in patients with postpartum anemia and blunted erythropoiesis. Eur J Clin Invest. 2000 Feb;30(2):154-61

BACKGROUND: To compare efficacy between recombinant human erythropoietin (rhEPO) plus parenteral iron vs. iron alone (parenteral vs. oral) in postpartum anaemia. METHODS: Sixty patients (haemoglobin 8.6 +/- 1.1 g dL-1) were randomized to rhEPO plus intravenous (i.v.) iron sucrose (group 1), rhEPO placebo plus i.v. iron sucrose (group 2), or oral iron alone (group 3), daily for 4 days beginning 48-72 h postpartum. Erythropoiesis and iron status were assessed before, and on 4, 7 and 14 days after, starting therapy. RESULTS: On day 7 the group 1 haematocrit increase was 7.7 +/- 3.1% vs. 5.3 +/- 1.9% (group 2, $P < 0.01$) and 4.4 +/- 3.2% (group 3, $P < 0.01$), and on day 14, 11.3 +/- 2.9% vs. 9.2 +/- 3.4% (group 2, $P < 0.05$) and 8 +/- 2.8% (group 3, $P < 0.01$). The odds of achieving a target haematocrit > 32% on day 7 and > 35% on day 14 were higher on rhEPO (1.5-2.7) than on either iron regimen alone. Group 1 reticulocyte counts were also higher on days 4 ($P < 0.05$ vs. oral iron) and 7 ($P < 0.01$ vs. oral and parenteral iron). CONCLUSION: All three regimens were effective in postpartum anaemia, but the haematocrit and reticulocyte responses to rhEPO plus parenteral iron were significantly greater than to iron alone. Benefit was greatest in the blunted erythropoiesis subgroup with elevated post-Caesarean section C-reactive protein levels.

Makrydimas G, Lolis D, Lialios G, Tsiara S, Georgiou I, Bourantas KL. Recombinant human erythropoietin treatment of postpartum anemia. Preliminary results. Eur J Obstet Gynecol Reprod Biol. 1998 Oct;81(1):27-31

OBJECTIVES: The aim of this study was to investigate the efficacy of recombinant human erythropoietin (rHuEpo) in postpartum anemia. STUDY DESIGN: At the University Hospital of Ioannina, rHuEpo was administrated subcutaneously to twenty anemic women (hemoglobin [Hb]<10 g/dl), for 15 days following delivery; all were given iron and folic acid per os. Twenty other women (the control group) with postpartum anemia (Hb<10 g/dl), received only iron and folic acid. The Mann-Whitney U-test was used for the comparison of hematological indices between the two groups, on days 1, 3, 5, 10, 15 and 40 postdelivery. RESULTS: On day 3, reticulocyte counts were significantly higher in the women who received rHuEpo, as compared to the controls ($P<0.05$). The mean Hb value increased to >2 g/dl in the group undergoing rHuEpo therapy as compared to 0.7 g/dl in the control group on day 5 ($P<0.05$). Furthermore, two women in the control group required blood transfusions, while no transfusions were required by the rHuEpo group. CONCLUSIONS: rHuEpo administration is useful for a more rapid amelioration of hematological indices in women with postpartum anemia. Further, the dose given in this study was not associated with significant side-effects.

- **Traitement des anémies chez les patients VIH**

L'anémie est fréquente chez les patients infectés par le VIH, d'autant plus que le stade de la maladie est avancé. L'anémie chez les patients VIH est associée à une diminution de la qualité de vie et une augmentation de la mortalité. D'autre part, le recours à la transfusion sanguine, parfois envisagé chez de tels patients, est associé à une augmentation de la mortalité.

La grande majorité des études sont des essais non randomisés en ouvert ou des études épidémiologiques.

Les critères d'inclusion des patients utilisés dans l'ensemble des études sont variables, l'anémie étant définie en fonction de l'hémoglobinémie ou de l'hématocrite avec des valeurs différentes. Les patients ont quasi-exclusivement une concentration sérique d'érythropoïétine endogène basse (≤ 500 UI/L).

Parmi les critères de non-inclusion, figuraient les anémies attribuables à une autre cause que l'infection par le VIH : une carence en fer, folates ou vitamine B12, une hémolyse, une perte sanguine aiguë ou chronique…

Les critères d'évaluation sont également variables selon les études : hémoglobinémie (ou hématocrite), mesure de la qualité de vie, besoins transfusionnels, taux de décès.

Les études montrent que le traitement par époétine- alfa permet une augmentation de l'hémoglobinémie de 2,5 g/dL et une amélioration des scores de qualité de vie chez les patients ayant une concentration sérique d'érythropoïétine endogène basse. Cependant l'effet du traitement sur la réduction des besoins transfusionnels ou le taux de mortalité n'est pas clairement établi.

En 2007, une méta-analyse de Cochrane a combiné les résultats de quatre essais randomisés, en double aveugle, contre placebo, chez des patients VIH anémiques traités par zidovudine. Cette méta-analyse ne permet pas de conclure à une réduction du nombre de transfusions sanguines.

En conclusion, il apparait que le traitement par érythropoétine n'est pas justifié chez les patients VIH atteints d'anémie modérée.

Une étude clinique de bonne qualité est souhaitable pour définir clairement les critères d'inclusion des patients qui tireraient un bénéfice du traitement (en fonction des concentrations d'érythropoéitine endogène ?...) et connaître les données de sécurité.

Dans l'attente de données supplémentaires, une prescription d'EPO serait possible sur justification dans le dossier du patient chez les patients à un stade avancé de SIDA, atteints d'une anémie sévère (Hb < 10 g/dL) et après diagnostic d'élimination, dans le but de réduire les transfusions sanguines (environ 1% des patients VIH, soit 1 000 patients au maximumen France).

Effet de l'EPO dans l'anémie du patient VIH

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Marti-Carvajal (2007)	**Cochrane sur 4 essais** Seuls les résultats de 3 essais sont retenus	EPO		[Hb] Besoins transfusionnels QdV	Résultats **NS** versus placebo . ↓ [Hb], . ↓ nombre de transfusion . Amélioration de la qualité de vie des patients HIV anémiés
Henry (1992)	**Méta-analyse** (4 essais cliniques randomisés en double aveugle) **N =297** (SIDA traité par	- Epoétine alfa : 100 à 200 U/kg x3/sem. - placebo	12 sem.	- [Hte] - Besoins transfusionnels - QdV	*Patients à bas taux d'EPO endogène (≤ 500 IU/L) (EPO : n=89 ; placebo : n=88) : - [Hte] : ↑ **S** : +3,9% (1,8 à 6,0 ; p<0,0002) - nombre d'unités de sang :

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
	zidovudine, Ht < 0,30)				transfusées : ↓**S** : -1,9 (-3,2 à -0,6 ; **p<0,003**) - QdV : **NS** * Patients à taux élevé d'EPO endogène (> 500 IU/L) (EPO : n=36 ; placebo : n=42) : - [Hte] : **NS** - nombre moyen d'unités de sang transfusées : **NS :** -0,2 (-1,3 à 1,7) - QdV : non analysée - Tolérance : pas de toxicité liée au traitement
Buskin (2004)	- **Etude épidémiologique descriptive longitudinale** (1996-2001) **N =596** (SIDA avec anémie, [Hb] < 10,5 g/dL) **dont n = 216** patients HIV très anémiés ([Hb] < 8.1g/dL) :	22% non traités, 42% transfusés, 12% époétine alfa, 24% époétine + transfusion	13 mois en moyenne	- Taux de décès	De 1996 à 2001 : incidence de l'anémie : ↓**S** de 13% à 5% **(p< 0.05)** Chez les patients dont les CD4 < 100/ml : - incidence plus élevée : 24-35% - pas de diminution de l'anémie Taux de mortalité : 37% . non traités : 13% . transfusés : 52% . époétine alfa : 19% . époétine + transfusion : 47% - Patients traités par EPO seule (n=27) : risque de décès non diminué : RR=1,1 (0,5 à 2,3) - Patients transfusés (n=91) : ↑ risque de décès : RR=3,2 (1,7 à 6,2)
Moore (1998)	- **Etude épidémiologique descriptive longitudinale** (1989-1996) **N=498** (SIDA avec anémie, Hb < 9,5 g/dL)	EPO	6 mois en moyenne (2 sem. à 28 mois)	- Taux de décès	Patients traités par EPO (n=91) : ↓ **S** risque de décès : RR=0,57 (0,40 à 0,81 ; p=0,002)
Grossman (2003)	**Randomisée** **Ouverte** **N =272** (Hb ≤ 12 g/dL)	- Epoétine alfa : 40 000 à 60 000 U x1/sem. - Epoétine alfa : 100 à 300 UI/kg x3/sem.	16 sem.	Primaire : - Mesure de la qualité de vie (MOS-HIV) Secondaire : - Mesure de la qualité de vie (LASA QdL) - [Hb] - Besoins transfusionnels - Tolérance	- QdV : améliorée pour les deux groupes par rapport à l'inclusion de S8 à S16 (excepté les items « fonction cognitive » et « douleur » pour le schéma 1x/sem. avec le MOS-HIV) - QdV : **NS** entre les deux groupes à S16. - [Hb] à la S16 (par rapport à l'inclusion) **NS** : - 1x/sem. : +2,9 g/dL - 3x/sem. : +2,5 g/dL - Corrélation entre l'augmentation de [Hb] et l'amélioration de QdV.
Phair (1993)	**Ouverte** **Multicentrique** **N = 1943**	rHuEPO : 4000 UI sc/ sem tous les 6 jours Selon la réponse, possibilité	54 sem	[Hte] Nbre de transfusion	- [Hte] : ↑ à S12 et S24. Réponse maintenue jusqu'à S54 - Patients transfusés : . A S6 : 40% . A S12 : 22% . A S24 : 18%

Auteur principal	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
		d'augmenter la dose sc à 8000 UI/sem tous les 6 jours			Effets indésirables : 11%
Saag (2004)	**Ouverte** **N =650** ([Hb] ≤11 g/dL)	Epoétine alfa : 40 000 à 60 000 UI x1/sem.	8 sem.	- [Hb] - Mesures de la qualité de vie (LASA QdV et MOS-HIV)	- QdV : ↑ **S (p<0,0001)** - [Hb] : ↑ **S** de 2,5 g/dL (2,3 à 2,6 ; **p<0,0001**) - Corrélation entre l'augmentation de l'hémoglobinémie et l'amélioration de la qualité de vie.
Levine 2008)	**Ouverte multicentrique** **N = 292** patients HIV avec [Hb] = 10, 8 g/dL, CD4 = 280/µl	Patients HIV avec [Hb] < 12 g/dl : époétine alfa : 40000UI sc 1x/sem pour atteindre Hb≥ 13 g/dL puis époétine en traitement d'entretien	24 sem	- [Hb] - QdV	. [Hb] ≥ 13 g/dL : 81% des patients . [Hb] ≥ 12g/dL : 92 % Bonne tolérance
Abrams (2000)	**Ouverte** **N =207**	Epoétine alfa : 100 à 300 U/kg x3/sem.	4 mois	- [Hb] - QdV	- [Hb] : ↑ **S** stable de 2,5 g/dL **(p<0,01)** - QdV :, ↑ **S** corrélés à l'hémoglobinémie
Lucas (2006)	**Ouverte** **Comparative** **N = 12** patients HIV hémodialysés	Epoétine alfa IV 2 à 3 x/ sem pdt 3 mois Puis darbepoetin alfa 1x/sem pdt 3 mois	6 mois	% de sujets [Hb] ≥ 11 g/dL	Des doses plus faibles et plus espacées de darbépoétine sont aussi efficaces que l'époétine alfa 2 à 3 x/sem à des doses plus élevées
Kimel (2008)	**Revue**	Le traitement de l'anémie des patients HIV par époétine alfa a un impact significatif sur la qualité de vie notamment sur la fatigue			

QdV : qualité de vie
Hte : hématocrite

Bibliographie

Les référentiels de la Juste prescription du CEDIT (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 1992.

1. Martí-Carvajal AJ, Solà I. Treatment for anemia in people with AIDS. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004776.

2. Henry DH, Beall GN, Benson CA, Carey J, Cone LA, Eron LJ, Fiala M, Fischl MA, Gabin SJ, Gottlieb MS, Galpin JE, Groopman JE, Hooton TM, Jemsek JG, Levine RL, Miles SA, Rinehart JJ, Rios A, Robbins WJ, Ruckdeschel JC, Smith JA, Spruance SL, Starrett B, Toney J, Zalusky R, Abels RI, Bryant EC, Larholt KM, Sampson AR, Rudnick SA. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. Ann Intern Med. 1992 Nov 1;117(9):739-48.

3. Buskin SE, Sullivan PS. Anemia and its treatment and outcomes in persons infected with human immunodeficiency virus. Transfusion. 2004 Jun;44(6):826-32.

4. Moore RD. Human immunodeficiency virus infection, anemia, and survival. Clin Infect Dis. 1999 Jul;29(1):44-9.

5. Grossman HA, Goon B, Bowers P, Leitz G; 010 Study Group. Once-weekly epoetin alfa dosing is as effective as three times-weekly dosing in increasing hemoglobin levels and is associated with improved quality of life in anemic HIV-infected patients. J Acquir Immune Defic Syndr. 2003 Dec 1;34(4):368-78.

6. Phair JP, Abels RI, McNeill MV, Sullivan DJ. Recombinant human erythropoietin treatment: investigational new drug protocol for the anemia of the acquired immunodeficiency syndrome. Overall results. Arch Intern Med. 1993 Dec 13;153(23):2669-75.

7. Saag MS, Bowers P, Leitz GJ, Levine AM; Community HIV Anemia Management Protocol Sites (CHAMPS) Study Group. Once-weekly epoetin alfa improves quality of life and increases hemoglobin in anemic HIV+ patients. AIDS Res Hum Retroviruses. 2004 Oct;20(10):1037-45.
8. Levine AM, Salvato P, Leitz GJ; Champs 2 Study Group. Efficacy of epoetin alfa administered every 2 weeks to maintain hemoglobin and quality of life in anemic HIV-infected patients. AIDS Res Hum Retroviruses. 2008 Feb;24(2):131-9.
9. Abrams DI, Steinhart C, Frascino R. Epoetin alfa therapy for anaemia in HIV-infected patients: impact on quality of life. Int J STD AIDS. 2000 Oct;11(10):659-65.
10. Lucas C, Carrera F, Jorge C, Boquinhas H, Pais MJ. Effectiveness of weekly darbepoetin alfa in the treatment of anaemia of HIV-infected haemodialysis patients.Nephrol Dial Transplant. 2006 Nov;21(11):3202-6.
11. Kimel M, Leidy NK, Mannix S, Dixon J. Does epoetin alfa improve health-related quality of life in chronically ill patients with anemia? Summary of trials of cancer, HIV/AIDS, and chronic kidney disease. Value Health. 2008 Jan-Feb;11(1):57-75.
12. Brokering KL, Qaqish RBManagement of anemia of chronic disease in patients with the human immunodeficiency virus. Pharmacotherapy. 2003 Nov;23(11):1475-85.
13. Volberding PA, Levine AM, Dieterich D, Mildvan D, Mitsuyasu R, Saag M; Anemia in HIV Working GroupAnemia in HIV infection: clinical impact and evidence-based management strategies. Clin Infect Dis. 2004 May 15;38(10):1454-63.

Résumé-Abstract

Martí-Carvajal AJ, Solà I. Treatment for anemia in people with AIDS. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004776.

BACKGROUND: Anemia is a common clinical disease in persons with HIV infection and is associated with poor prognosis. There is a need to assess the effects of anemia treatments, and to determine whether these interventions are beneficial. OBJECTIVES: To determine the efficacy and safety of treatments for anemia in people with HIV infection and AIDS. SEARCH STRATEGY: The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2005), MEDLINE (1980-July 2005), EMBASE (1980-July 2005), LILACS (1982 to July 2005), reference lists of relevant articles and contact with authors. See Cochrane HIV/AIDS Group search strategy. SELECTION CRITERIA: Randomized trials assessing the effects of treatments for anemia in people diagnosed with HIV infection. There were no age restrictions. DATA COLLECTION AND ANALYSIS: Both authors independently assessed relevant studies for inclusion. Data extraction and quality assessment of relevant studies was performed by one author and checked by the other author. MAIN RESULTS: We included four trials, but focused on the results based on three trials with acceptable attrition rate. None of the trials reported data on death. The two trials that compared recombinant human erythropoietin (rHuEPO) to placebo did not show any benefit on hematological values response, number of patients transfused, or number of packed red cell transfused. One trial compared the effects of two rHuEPO dosing regimens on hemoglobin value and quality of life, but the effects are unclear. AUTHORS' CONCLUSIONS: There is a lack of reliable evidence on interventions for treating anemia in patients with HIV infection. This Cochrane review has found some evidence that rHuEPO reduces transfusion requirements, increases hemoglobin levels, and improves quality of life in HIV-infected patients with anemia. However, this is based on evidence from randomized trials with weak or poor methodological quality. There is a need for randomized trials of high methodological quality to evaluate the effect of interventions on anemia in persons infected with human immunodeficiency virus.

Henry DH, Beall GN, Benson CA, Carey J, Cone LA, Eron LJ, Fiala M, Fischl MA, Gabin SJ, Gottlieb MS, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. Ann Intern Med. 1992 Nov 1;117(9):739-48.

OBJECTIVE: To assess the effect of recombinant human erythropoietin (r-HuEPO) on anemia in patients with the acquired immunodeficiency syndrome (AIDS) who are receiving zidovudine therapy. DESIGN: Combined analysis of four 12-week, randomized, double-blind, controlled clinical trials. SETTING: Multiple centers in the United States. PATIENTS: Two hundred and ninety-seven anemic (hematocrit < 30%) patients with AIDS who were receiving zidovudine therapy. Of the 297 patients, 255 were evaluable for efficacy, but all patients were included in analysis of safety. INTERVENTION: Patients were randomly assigned to receive either r-HuEPO (100 to 200 U/kg body weight) or placebo, intravenously or subcutaneously, three times per week for up to 12 weeks. MEASUREMENTS: Changes in mean hematocrit, transfusion requirement, and quality of life. RESULTS: Sixty-nine percent of patients had endogenous serum erythropoietin levels less than or equal to 500 IU/L, and 31% had erythropoietin levels greater than 500 IU/L. In patients with low erythropoietin levels (< or equal to 500 IU/l), r-HuEPO therapy decreased the mean number of units of blood transfused per patient when compared with placebo (3.2 units and 5.3 units, respectively; P = 0.003) and increased the mean hematocrit from the baseline level (4.6 percentage points and 0.5 percentage points, respectively; P <0.001). Overall quality of life improved in patients on r-HuEPO therapy (P = 0.13). Patients with erythropoietin levels greater than 500 IU/L showed no benefit from r-HuEPO in any outcome variable. Placebo and r-HuEPO recipients did not differ in the incidence of adverse effects or opportunistic infections. CONCLUSION: Therapy with r-HuEPO can increase the mean hematocrit and decrease the mean transfusion requirement in anemic patients with AIDS who are receiving zidovudine and have endogenous low erythropoietin levels (< or equal to 500 IU/L). Such therapy is of no apparent benefit in patients whose endogenous erythropoietin levels are higher than 500 IU/L.

Buskin SE, Sullivan PS. Anemia and its treatment and outcomes in persons infected with human immunodeficiency virus. Transfusion. 2004 Jun;44(6):826-32.

BACKGROUND: Anemia is a common comorbidity with HIV. Before the highly active antiretroviral therapy (HAART) era, anemia was found to be associated with decreased survival. This study examined the prevalence of anemia since HAART's availability and the associations between anemia treatments and survival. STUDY DESIGN AND METHODS: Anemia prevalence in a cohort of HIV-infected persons was described. In a smaller cohort of HIV-infected anemic patients, survival was modeled with a time-dependent proportional hazards regression model adjusting for CD4+ T-lymphocyte count, plasma HIV RNA concentration load, hemoglobin (Hb) level, and other factors. RESULTS: Anemia (Hb level < 10.5 g/dL, or physician diagnosis) decreased from 13 to 5 percent ($p < 0.05$) in 1996 through 2001. Anemia prevalence was highest (24-35%) and did not decrease among patients with CD4 count less than 100 cells per mL. In total, 216 severely anemic HIV-infected individuals (mean Hb level, 8.1 g/dL) followed for a median of 13 months had a 37-percent mortality rate. Of these, 22 percent were untreated (13% mortality rate), 42 percent received transfusion alone (52% mortality), 12 percent received epoetin alfa alone (19% mortality), and 24 percent received both (47% mortality). Transfusion was associated with a threefold excess mortality risk, but epoetin alfa prescription was not associated with mortality. CONCLUSION: The prevalence of anemia decreased in the HAART era, and transfusion was positively associated with risk of death, suggesting limiting use of transfusions in nonemergency situations.

Moore RD. Human immunodeficiency virus infection, anemia, and survival. Clin Infect Dis. 1999 Jul;29(1):44-9.

Anemia, a common hematologic complication in human immunodeficiency virus (HIV)-infected patients, can be caused by mechanisms including infections, neoplasms, or drug treatment. Studies have consistently found anemia to be associated with reduced survival, even when potentially confounding factors were controlled for. Importantly, recovery from anemia has been shown to reduce this risk to approximately the same level as seen among patients never having had anemia. Although anemia traditionally has been treated with blood transfusions, recent studies have shown recombinant human erythropoietin (r-HuEPO) to be effective in elevating hematocrit values and reducing transfusion requirements in HIV-infected patients who have endogenous erythropoietin levels of < or = 500 IU/L. Therapy with r-HuEPO has been shown to be safe and well tolerated. In a recent study, moreover, receipt of erythropoietin was associated with a decreased risk of death, whereas transfusion was associated with an increased risk. If these results are confirmed, the link between r-HuEPO and decreased risk of death in HIV-infected patients with anemia will be further strengthened.

Grossman HA, Goon B, Bowers P, Leitz G; 010 Study Group. Once-weekly epoetin alfa dosing is as effective as three times-weekly dosing in increasing hemoglobin levels and is associated with improved quality of life in anemic HIV-infected patients. J Acquir Immune Defic Syndr. 2003 Dec 1;34(4):368-78.

BACKGROUND: Anemia is prevalent in HIV-positive patients despite lower doses of zidovudine used in highly active antiretroviral therapy. Previously, epoetin alfa has been administered 3 times weekly (TIW). We compared the hematologic and quality of life (QOL) effects and tolerability of the more convenient once-weekly (QW) regimen with TIW epoetin alfa in anemic HIV-positive patients. METHODS: Two hundred eighty-five anemic (hemoglobin [Hb] <12 g/dL) HIV-positive adults receiving stable antiretroviral therapy were enrolled in this 16-week, randomized, multicenter study. Enrolled patients were randomized to receive epoetin alfa doses of 40,000 to 60,000 U QW or 100 to 300 U/kg TIW. RESULTS: Two hundred seventy-two patients were evaluable for efficacy. Both epoetin alfa dosing schedules produced significant Hb level increases by week 2 (mean Hb increase of 1.3 g/dL [QW] and 1.0 g/dL [TIW]; $P < 0.0001$) that continued to increase until week 8 and were maintained until study completion, with no significant difference between treatment groups at final Hb measurement (mean Hb increase of 2.9 g/dL [QW] and 2.5 g/dL [TIW]). All QOL parameters improved significantly ($P < 0.05$) from baseline by week 8 in both groups, with no significant differences between groups at week 16. Both dosing schedules were well tolerated. CONCLUSIONS: QW dosing of epoetin alfa is as effective as TIW dosing in increasing Hb levels, which was associated with improved QOL in anemic HIV-positive patients. QW dosing should also offer added convenience for patients and caregivers.

Phair JP, Abels RI, McNeill MV, Sullivan DJ. Recombinant human erythropoietin treatment: investigational new drug protocol for the anemia of the acquired immunodeficiency syndrome. Overall results. Arch Intern Med. 1993 Dec 13;153(23):2669-75.

BACKGROUND : Anemia associated with human immunodeficiency virus infection may be due to reduced erythropoiesis related to the disease itself or to concomitant medications (eg, zidovudine). Clinical studies have shown recombinant human erythropoietin (r-HuEPO) to be effective in correcting the anemia of zidovudine-treated patients infected with human immunodeficiency virus with baseline serum erythropoietin levels of 500 U/L or less. A treatment investigational new drug protocol that provided r-HuEPO to 1943 anemic patients with the acquired immunodeficiency syndrome was studied. METHODS: Enrollment criteria included a clinical diagnosis of acquired immunodeficiency syndrome, serum erythropoietin level of 500 U/L or less, hematocrit less than 0.300,

and age of 12 years or more. The initial r-HuEPO dosage was 4000 U subcutaneously for 6 days each week. On the basis of response, the r-HuEPO dosage could be increased sequentially to 8000 U subcutaneously for 6 days per week. This was an open-label multicenter treatment protocol. A total of 1943 patients were treated by 510 investigators. Efficacy evaluations were based on the effect of r-HuEPO on hematocrit levels and transfusion requirements relative to baseline. Adverse experiences that were considered by the investigator to be possibly related to r-HuEPO therapy were collected to assess safety. RESULTS: Therapy with r-HuEPO resulted in an increase in mean hematocrit from a baseline of 0.280 to 0.331 at week 12 and 0.338 at week 24. This increase was sustained throughout the course of the study to week 54. Overall, 40% of patients (769/1943) required at least one transfusion in the 6-week interval immediately preceding study entry (baseline). After 12 and 24 weeks of r-HuEPO treatment, corresponding percentages were 22% (311/1387) and 18% (119/650), respectively. Response to therapy, defined as an increase of 0.060 from baseline in hematocrit, with no transfusions within 28 days before achieving that hematocrit, was observed in 44% of patients. Adverse experiences not clearly related to acquired immunodeficiency syndrome were reported by 11% of patients. CONCLUSION: In a study population of 1943 anemic patients with acquired immunodeficiency syndrome treated with r-HuEPO, the hematocrit increased and blood transfusion requirements decreased. Therapy with r-HuEPO was well tolerated.

Saag MS, Bowers P, Leitz GJ, Levine AM; Community HIV Anemia Management Protocol Sites (CHAMPS) Study Group. Once-weekly epoetin alfa improves quality of life and increases hemoglobin in anemic HIV+ patients. AIDS Res Hum Retroviruses. 2004 Oct;20(10):1037-45.

This prospective, open-label, multicenter trial evaluated the effects of once-weekly (qw) epoetin alfa on quality of life (QOL) and hemoglobin (Hb) levels in anemic human immunodeficiency virus (HIV)-infected adult receiving antiretroviral therapy. A total of 650 patients with Hb < or = 11 g/dl received epoetin alfa 40,000 U qw subcutaneously, with dose escalation to 60,000 qw if Hb increase was <1 g/dl after 4 weeks. The linear Analog Scale Assessment (LASA) overall QOL score, LASA energy score, and LASA activity score each significantly improved from baseline to final measurement ($p < 0.0001$ for each parameter). Improvements in the Medical Outcomes Study (MOS)-HIV physical and mental health summary scores were also significant ($p < 0.0001$), and coincided with Hb increases. Mean Hb increased from baseline to final measurement by 2.5 g/dl (95% CI: 2.3, 2.6 g/dl; $p < 0.0001$). Objective hematological response rate, defined as a > or = 1 g/dl Hb increase from baseline to week 8, was 86%. Hemoglobin increased significantly in all subgroups of race, zidovudine use, CD4+ cell count, and viral load. Once-weekly epoetin alfa was well tolerated. Once-weekly epoetin alfa is effective in improving QOL and Hb measures.

Levine AM, Salvato P, Leitz GJ; Champs 2 Study Group. Efficacy of epoetin alfa administered every 2 weeks to maintain hemoglobin and quality of life in anemic HIV-infected patients. AIDS Res Hum Retroviruses. 2008 Feb;24(2):131-9.

Anemia, a common hematological abnormality in HIV, contributes to decreased quality of life (QOL). This study assessed once-every-2-week epoetin alfa on maintaining QOL and hemoglobin (Hb) in anemic HIV-infected patients in a 24-week, open-label, multicenter study. HIV-infected patients (Hb < or =12 g/dl) received epoetin alfa 40,000 units subcutaneously once weekly, until reaching Hb > or =13 g/dl. Patients then entered a maintenance phase (MP), in which epoetin alfa was administered every other week or at longer intervals. The trial objectives were to determine if QOL, as measured by the Medical Outcomes Study-HIV (MOS-HIV) general health perceptions (GHP) domain and Hb, was maintained. Safety was also assessed. A total of 292 patients were enrolled (72% on HAART). Mean baseline laboratory values were Hb = 10.8 g/dl, CD4(+) count = 280 cells/microl, and HIV RNA = 51,867 copies/ml. In all, 81% of patients reached Hb > or =13 g/dl and 92% reached Hb > or =12 g/dl. QOL was maintained from the beginning (GHP = 44.2 points) to the end of MP (GHP = 43.4 points) with every other week or longer dosing. Mean Hb at the beginning of MP was 13.4 +/- 0.5 g/dl and was 12.8 +/- 1.4 g/dl at study end. Epoetin alfa was well tolerated; adverse events were consistent with those reported in previous studies of epoetin alfa in HIV-infected patients. Although the clinical approach tested in this study is not consistent with current prescribing recommendations, the results confirm the efficacy of prolonged dosing intervals (every 2-4 weeks) in maintaining optimal Hb levels and QOL in anemic HIV-infected patients.

Abrams DI, Steinhart C, Frascino R. Epoetin alfa therapy for anaemia in HIV-infected patients: impact on quality of life. Int J STD AIDS. 2000 Oct;11(10):659-65.

To evaluate the effect of epoetin alfa on the quality of life (QOL) of HIV-infected patients in the community setting, 221 anaemic (haemoglobin < or = 11 g/dl) HIV-positive patients from community-based treatment centres and physicians' offices were treated with epoetin alfa (100-300 units/kg subcutaneously 3 times a week) in a 4-month, open-label, non-randomized, phase IV trial. Epoetin alfa therapy significantly ($P<0.01$) increased and maintained haemoglobin levels (mean increase=2.5 g/dl; n=207); the improvement in haemoglobin levels was independent of changes in CD4+ cell counts. Transfusion requirements were also significantly reduced from 20% to 5% of patients ($P<0.01$). Mean total QOL score measured by the Functional Assessment of HIV Infection (FAHI) scale and Physical Well-Being subscale score improved significantly ($P<0.05$). QOL improvements associated with

increases in haemoglobin were independent of changes in CD4+ counts and baseline anaemia severity. Adverse events observed during epoetin alfa therapy were consistent with HIV disease and not likely due to the drug. Epoetin alfa therapy should be considered a treatment option for HIV-infected patients with mild-to-moderate anaemia.

Lucas C, Carrera F, Jorge C, Boquinhas H, Pais MJ. Effectiveness of weekly darbepoetin alfa in the treatment of anaemia of HIV-infected haemodialysis patients.Nephrol Dial Transplant. 2006 Nov;21(11):3202-6.

BACKGROUND: Anaemia is aggravated by the coexistence of chronic kidney disease (CKD) in patients infected with human immunodeficiency virus (HIV). Darbepoetin alfa effectively alleviates CKD-associated anaemia with less frequent dosing than recombinant human erythropoietin (EPO). The current study aimed to determine the efficacy, safety and cost-effectiveness of darbepoetin alfa compared with erythropoietin alfa (EPO-alfa) for treatment of anaemia in HIV-infected subjects receiving haemodialysis. METHODS: An open label, single arm, prospective study of 12 haemodialysis subjects with HIV infection was conducted for a duration of 6 months after switching from intravenous (i.v.) EPO-alfa two/three times weekly to i.v. darbepoetin alfa once weekly. The primary end point was the proportion of patients maintaining haemoglobin (Hb) levels>or=11 g/dl while a weekly dose of darbepoetin alfa was a secondary end point. RESULTS: Darbepoetin alfa, as effectively as EPO-alfa maintained the proportion of the subjects having Hb levels>or=11 g/dl at an average weekly dose of 40.60 microg compared with an equivalent dose of 51.84 microg for EPO-alfa. Antiretroviral therapy and HIV infection stage remained the same for each specific patient throughout the study period, including the last 6 months of EPO-alfa therapy. No difference in the incidence of adverse effects was observed after switching from EPO-alfa to darbepoietin alfa. CONCLUSIONS: Lower doses of darbepoetin alfa at extended dosing interval is as safe and effective as EPO-alfa for treating anaemia, suggesting that darbepoetin alfa is a more cost-effective therapeutic alternative to EPO-alfa in the management of anaemia associated with HIV infection in subjects receiving haemodialysis.

Kimel M, Leidy NK, Mannix S, Dixon J. Does epoetin alfa improve health-related quality of life in chronically ill patients with anemia? Summary of trials of cancer, HIV/AIDS, and chronic kidney disease. Value Health. 2008 Jan-Feb;11(1):57-75.

OBJECTIVES: Anemia, defined as having low levels of hemoglobin (HGB), is caused by disease-related (e.g., bone marrow suppression, nutritional deficiency) or treatment-related (e.g., chemotherapy, antiretroviral therapy) factors. Although epoetin alfa has been shown to improve HGB outcomes in cancer, HIV/AIDS, and chronic kidney disease (CKD), these results have been viewed in isolation, rather than across populations. The purpose of this article is to review findings from trials that evaluated the impact of epoetin alfa on HGB and health-related quality of life (HRQL) across various populations with different underlying causes of anemia. METHODS: A review of clinical trials published in English between January 1993 and September 2005. Searches were conducted using MEDLINE and EMBASE. Between- and within-group changes in HGB and HRQL were examined. RESULTS: One hundred ten articles were retrieved and 18 were reviewed. Statistically significant improvements in HGB were generally seen (1) between groups for cancer patients receiving epoetin alfa compared with those receiving placebo or standard of care (SOC) (between-group differences in changes from baseline to end point ranging from 1.2 to 1.9 g/dl); and (2) within groups for HIV/AIDS and CKD patients receiving epoetin alfa (changes from baseline to end point of 2.5 and 2.9 g/dl and 2.7 g/dl, respectively). Statistically and clinically significant improvements in HRQL, particularly with regard to fatigue, were seen across chronic conditions based on the Linear Analog Scale Assessment energy scale; where improvements of at least 8 mm-considered clinically relevant-were generally seen (1) between groups for cancer patients receiving epoetin alfa compared with those receiving placebo or SOC (differences in changes from baseline to end point from 0.8 to 19.8 mm); and (2) within groups for HIV/AIDS and CKD patients receiving epoetin alfa (changes from baseline to end point of 23 and 25 mm and 28 mm, respectively). CONCLUSIONS: Results of published clinical trials suggest that treatment of anemia associated with cancer, HIV/AIDS and CKD can have a significant impact on HRQL, particularly fatigue, and that this impact is both statistically and clinically significant.

Brokering KL, Qaqish RBManagement of anemia of chronic disease in patients with the human immunodeficiency virus. Pharmacotherapy. 2003 Nov;23(11):1475-85.

Anemia is the most frequently encountered hematologic complication in human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome. The prevalence estimates vary widely with the severity of HIV disease. Data suggest that treatment with highly active antiretroviral therapy may have a positive impact on reducing the prevalence of anemia of chronic disease in patients infected with HIV. Anemia consistently has been shown to be a predictor of decreased survival, and treatment plays an important role in improving patients' survival and quality of life (e.g., fatigue and dementia). Addressing potential underlying reversible causes and treating the chronic anemia are important strategies in the management of anemia. Erythropoietin therapy should

be considered a first-line treatment, and blood transfusions should be limited to situations requiring immediate correction of hemoglobin levels.

Volberding PA, Levine AM, Dieterich D, Mildvan D, Mitsuyasu R, Saag M; Anemia in HIV Working GroupAnemia in HIV infection: clinical impact and evidence-based management strategies. Clin Infect Dis. 2004 May 15;38(10):1454-63.

Anemia in human immunodeficiency virus (HIV)-infected patients can have serious implications, which vary from functional and quality-of-life decrements to an association with disease progression and decreased survival. In 2002, 16 members of the Anemia in HIV Working Group, an expert panel of physicians involved in the care of HIV-infected patients that met first in 1998, reconvened to assess new data and to translate these data into evidence-based treatment guidelines. The group reached consensus on the prevalence of anemia in the highly active antiretroviral therapy era; the risk factors that are independently associated with the development of anemia; the impact of anemia on quality of life, physical functioning, and survival; the impact of the treatment of hepatitis C virus coinfection on anemia in HIV-infected patients; evidence-based guidelines for treatment of anemia in HIV-infected patients, including the therapeutic role of epoetin alfa; and directions for future research.

- **Anémie des patients en insuffisance cardiaque chronique**

Les études publiées montrent que l'administration d'EPO dans l'insuffisance cardiaque entraine une augmentation de la contrentration d'hémoglobine et de l'hématocrite avec une amélioration des paramètres fonctionnels de la qualité de vie. La correction de l'anémie permet une amélioration de certains paramètres cardiovasculaires chez le patient insuffisant cardiaque chronique.

Les études randomisées versus placebo ne montrent pas de résultats significatifs et les études randomisées ouvertes ne mettent en évidence qu'un bénéfice fonctionnel douteux.
Le seuil et la cible d'Hb sont difficiles à déterminer et diffèrent selon les études.

L'étude de Van Veldhuisen de 2007 randomisée en double aveugle versus placebo chez 165 patients non dialysés modérément anémiés ([Hb] = 11.5 g/dL) montre une surmortalité dans le groupe traité par darbepoéitine. Cependant, les dernières données publiées ne mettent pas en évidence de risque cardio-vasculaire particulier chez les insuffisants cardiaques (HTA, thrombose). La méta-analyse de Van der Meer manque de puissance pour évaluer l'éventuel excès de risque d'AVC dans cette population (à l'instar de ce qui a été démontré récemment chez les insuffisants rénaux).

Il existe une insuffisance des données pour évaluer le rapport bénéfice/risque de l'EPO en cas d'anémie chez l'insuffisant cardiaque.

Deux études sont sont en cours dans cette situation :

- l'étude RED-HF (phase III) randomisée double-aveugle versus placebo devrait inclure 2600 patients (NYHA classe II-IV, FE < ou = 40% et [Hb] < ou = 12 g/dL et > 9 g/dL). Son objectif est de déterminer l'effet de la darbopoétine alfa sur la réduction de la morbi-mortalité et l'amélioration de la qualité de vie chez les patients insuffisants chroniques et anémiés ; le critère d'évaluation primaire est le délai jusqu'au décès toute cause ou 1ère hospitalisation pour aggravation de l'insuffisance cardiaque.
- l'étude IRON-HF, multicentrique randomisée en double-aveugle versus placebo est également en cours de recrutement chez les patients patients insuffisants cardiaques anémiés. Son objectif primaire est d'évaluer l'impact de la supplémentation en fer IV versus placebo chez les patients insuffisants cardiaques anémiés avec un déficit en fer.

Chez les patients insuffisants cardiaques avec une insuffisance rénale, l'utilisation de l'EPO relève de l'AMM.

Effet de l'EPO dans le traitement de l'anémie de l'insuffisant cardiaque chronique

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Van der Meer (2009)	**Méta-analyse de 7 études randomisées contrôlées versus placebo : N = 650** patients insuffisants cardiaques chroniques anémiés EPO : n = 363 Pla : n = 287			Hospitalisation Mortalité HTA Thromboses veineuses	Hospitalisation : risque diminue : ↓ **S** (RR = 0, 59/ 95% IC 0,41- 0,86 ; **p = 0,006**) Mortalité : **NS** (RR = O, 69 ; 95% IC 0, 39-1,23 ; **p = 0,21**) HTA : **NS** Thromboses veineuses : **NS**
Tehrani (2009)	**Méta-analyse de 7 études prospectives contrôlées** **N = 663** patients insuffisants cardiaques chroniques anémiés			. [Hb] . Durée d'exercice . la classe selon la classification de la New york Heart Association (NYHA) . Distance de marche sur 6 minutes . BNP	- [Hb] : ↑ **S** 95% IC [1.76-2.93] : **p < 0.00001** - Durée d'exercice : ↑ **S** IC 95% [0.08-1.73] : **p = 0.03** - Classe de la classification NYHA : Amélioration **S** : IC 95% [-2.32, -0.6] **p < 0.0009** - Distance de marche sur 6 minutes : ↑ **S** 95% IC [0.31, 2.54] **p = 0.03** - BNP : ↓ **S** IC 95% [-1.03, -0.06] **p =0.01**
Ghali (2008)	**Randomisée, double aveugle versus**	Darbepoetin alfa : 0.75 µg/kg sc toutes les 2 sem pdt 1 an	1 an	**Critère primaire :** A S27 : modification du temps du test d'effort	A S27 : [Hb] : ↑ **S** de 1,8 g/dL versus pla : **p < 0,001**

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
	placebo **N = 319** patients insuffisants cardiaques chroniques anémiés Darbépoétine : n = 162 Pla : n = 157 Stamina-HeFT, Phase II			**Critères secondaires :** A S27 : modification de : - la classe selon la classification de la New york association - QdV **Délai jusqu'au décès** quelle que soit la cause Ou délai jusqu'à la première hospitalisation due à l'insuffisance cardiaque	Après une analyse "en intention de traitement" : - Temps d'exercice : **NS** - Classe de la NYHA : **NS** - QdV : **NS** Tendance **NS** : risque moins élevé de mortalité toute cause ou de 1ère hospitalisation pour insuf cardiaque Evènements indésirables : **NS**
Van veldhuisen 2007	**Contrôlée randomisée, double aveugle vs placebo** **N=165** ICC depuis > 3 M Anémie modérée [Hb] =11.5 g/dL	Darbepoetin alfa sc toutes les 2 sem pdt 26 sem 0.75 ou 0.50 µg/kg	26 sem	- [Hb] (cible=14 g/dL) - tests fonctionnels (test de marche et QdV)	Gpe EPO : - [Hb] : ↑ **S** - Amélioration fonctionnelle **S** que sur 1 critère sur 5 - Amélioration **S** du questionnaire de cardiomyopathie (Kansas City) : 8.2 vs 1.5 points - EPO : 6 morts Pla : 0
Ponikowski 2007	**Comparative randomisée, double aveugle vs placebo** **N=41** 9 ≤[Hb]≤12 g/dL	Darbepoetin alfa 0.75 µg/kg sc toutes les 2 sem. pendant 26 sem.	30 sem	- Critère principal : VO2 en ml/kg/min - Autres critères : Volume absolu d'O2, durée de l'exercice, [Hb] et qualité de vie.	- VO2 : modification **NS** - durée de l'exercice au cours du test d'effort à S27 : **NS** - [Hb] : ↑ **S (p=0.0005)** à S27 - QdV (PGA) : amélioration KCCQ et MLHFQ): **≠ NS**
Kourea (2008)	**Randomisée versus placebo** **N = 41** Insuffisants cardiaques Classe NYHA : II-III FEVG < 40% [Hb] < 12.5 g/dL Creat < 2.5 mg/dL	Darbepoetin alfa : 1.5 µg/kg tous les 20j pdt 3 mois + Fer PO : n = 21 Pla + Fer PO : n = 20	3 mois	- Critères échographiques : . Fonction VG systolique et diastolique - BNP : peptide natriurétique de type B plasmatique - Distance parcourue à pieds sur 6 minutes (6MWT) - [Hb] - Marqueurs inflammatoires : TNF, IL6, CRP - Cytokine anti-inflammatoire : IL-10 Molécules d'adhésion endothéliale : ICAM-1 et VCAM-1 - Médiateurs solubles de l'apoptose **:** Ligand FAS soluble	<u>Gpe darbépoétine</u> : **-** BNP : ↓ **S (p= 0.002)** **-** IL-6 : ↓ **S (p = 0.013)** **-** ligand Fas soluble : ↓ **S (p= 0.023)** - FEVG : ↑ **S (p< 0.001)** **-** [Hb] : ↑ **S (p < 0.001)** **-** 6MWT : ↑ **S (p < 0.01)** <u>Gpe Pla</u> : Tous les critères : **NS** sauf 6MWT ↑ **S (p = 0.044)**

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
Kourea (2008)	**Randomisée versus placebo** **N = 41** Insuffisants cardiaques Classe NYHA : II-III FEVG < 40% [Hb] < 12.5 g/dL Creat < 2.5 mg/dL	Darbepoetin alfa : 1.5µg/kg tous les 20j pdt 3 mois + Fer PO : n = 21 Pla + Fer PO : n = 20	3 mois	Paramètres échographiques : - FEVG - QdV - BNP - 6MWT	Gpe darbépoétine : Amélioration : ↑ **S** . FEVG : **p < 0.001** . 6MWT : **p <0.01** . [Hb] : **p < 0.001** . BNP : **p =0.002** . Gpe pla : **NS**
Parissis (2008)	**Randomisée versus placebo** **N = 32** patients insuffisants cardiaques chroniques Darbépoétine alfa + fer : n = 21 Pla + fer : n = 11	Darbepoetin alfa : 1,5 µg/kg tous les 20 jours pdt 3 mois + Fer PO Pla + fer PO		- Critères échographiques : Fonction VG systolique et diastolique . Fonction VD - BNP : peptide natriurétique de type B plasmatique - Distance de marche sur 6 minutes	Gpe darbépétine : - Fonction VG : **amélioration S** des critères échographiques - Fonction VD : **amélioration S** **-** Classe NYHA **: amélioration S (p = 0,001)** **-** BNP plasmatique **: S (p = 0,001)** **-** Test de la marche sur 6 minutes : **S (p < 0, 001)** Gpe Pla : Tous les critères : **NS**
Mancini, 2003	**Contrôlée, randomisée, simple aveugle, vs placebo** **N=26** - n=12 traités - n=14 placebo ICC classe III à IV Ht<35%	Darbepoetin alfa sc: 5 000 U 3 fois/sem. pdt 4 sem. Si ↑ de l'Hb<1g/dL alors↑ de la dose à 10 000 U 3 fois/sem. pendant 3 mois	3 mois	- paramètres sanguins : [Hb], [Hte], vol plasm. - paramètres fonctionnels : VO2 et durée de l'effort - Capacité oxydative du muscle - qualité de vie	- ↑ **S** de [Hb] **(p=0.0001),** ↓ du vol. plasm. et ↑du nombre de GR - pic de VO2 : ↑ **S** - durée d'exercice : ↑ **S p<0.004** - **≠ NS** de la capacité oxydative du muscle - QdV : ↑ **S p<0.04**
Silverberg, (2001)	**Contrôlée randomisée vs placebo** **N=16** 10 ≤[Hb]<11.5 g/dL ICC de classe III à IV FEVG <40%	EPO 4 000 U/sem. sc la première sem. puis ajustée pour atteindre [Hb]=12.5 g/dL	5 à 12 mois	- [Hb] et [Hte] - Effet sur la fonction cardiaque : classe d'ICC, FEVG - Effet sur la fonction rénale - Nombre de j d'hosp. - Mortalité	- [Hb] : ↑ **S** - dose de furosémide, créatinine sérique, FEVG et du nombre de j d'hosp. : ↓ **S** - classe d'ICC : ↓ **S (p<0.0001)** - Pla : 4 morts - EPO : 0 décès
Palazzuoli (2006)	**Randomisée double aveugle versus placebo** **N = 40** patients en insuffisance cardiaque congestive avec Hb< 11g/dL	Epoétine bêta : 2X semaine pdt 3 mois + Fer 1x/j per os	12 mois	. [Hb] . Amélioration dans le classement fonctionnel de la NYHA . Temps d'endurance pdt le test d'effort . Distance parcourue pdt le test d'effort . VO2 pdt la phase d'oxygénation . VO2 au seuil anaérobique . Peptide natriurétique de type B plasmatique	**Gpe traité : ↑ S :** **-** [Hb] - amélioration du classement fonctionnel **-** temps d'endurance, distance parcourue **- VO2** pdt la phase d'oxygénation et au seuil anaérobique Peptide natriurétique de type B ↓ **S** **Gpe non traité : NS** Maintien du taux élevé [Hb] du gpe traité versus gpe placebo pdt les 9 mois suivants le traitement
Silverberg,	**Ouverte**	Darbepoetin alfa sc 1	1 an	- [Hb]	Dans les 2 gpes traités **:**

Auteurs	Type d'étude	Posologie	Suivi	Critères d'évaluation	Résultats
(2003)	**N=179** gpe1 = 84 diab type II gpe2 = 95 non diab. ICC classe III à IV [Hb] = [9.5-11.5 g/dL]	à 3 fois/sem. pour une [Hb] à 12.5 g/dL 1er sem:4 000/5 000 UI/ sem puis ↑ 10 000 UI/sem		- FEVG	- [Hb], classe d'ICC, FEVG : ↑ **S** [Hb] : . Gpe1 : ↑de 10.4 à 13.1 g/dL . Gpe 2 : ↑ de 10.5 à 12.9 g/dL - Amélioration des classes d'ICC de 34.8 et 32.4 % - nbre de j d'Hosp : ↓ **S** - taux de mortalité ↓ de 30 à 10%
Silverberg (2001)	**Ouverte** **N=126** ICC : III à IV [Hb] ≤11.5 g/dL	EPO sc 4 000 à 5 000 UI/sem. Puis ↑ à 2-3/sem.	5 à 27 mois	- Déterminants biologiques et cardiaques - QdV - Nombre d'hosp.	- [Hb] : ↑ **S** de 10.3 à 13.1 g/dL - [Hte] : ↑ **S** de 30.6 à 41.8% **(p<0.05)** - classe d'ICC : amélioration **S** de 3.7 à 2.3 % - FEVG : ↓ **S (p<0.05)** - Etat de fatigue et capacité respiratoire : amélioration **S** (index de VAS/SOB) **(p<0.01)** - nombre d'hosp : ↓ **S** de 3.7 à 0.2 **(p<0.05)**
Silverberg (2005)	**Ouverte** **N=78** [Hb] <12 g/dL	Epoétine bêta sc 5 000 à 10 000 U/sem. dose ↑ de 50% si [Hb] ↑ de moins de 1 g/dL	6 – 48 mois	- évolution d['Hb] et de la fonction cardiaque (classe ICC et FEVG)	. [Hb] : ↑ **S** de 10.2 à 13.5 g/dL **(p<0.01)** . classe d'ICC : ↓ **S** de 3.7 à 2.5 **(p<0.01)** - nombre de j d'Hosp : ↓ **S** de 2.7 à 0.7 j **(p<0.01)** - Clcr : **≠ NS**
Silverberg (2000)	**Rétrospective** **26/142 patients** [Hb] <12 g/dL et ICC 47% de classe IV FEVG <35%	EPO sc 2 000 U/sem. et dose ajustée pour [Hb]=12g /dL	7.2 +/- 5.5 mois	- Effet de la correction de l'anémie sur la fonction cardiaque, rénale et le nombre de jours d'hospitalisation.	- [Hb] et [Hte] : ↑ **S (p<0.001)** - Amélioration de la fonction cardiaque : . classe d'ICCC : ↓ de 79.1 % . FEVG : ↑ **S (p<0.001)** - nombre d'hosp : ↓ **S** (p<0.05).
Mc-Murray (2009)	Red-HF : en cours de recrutement (phase III) Objectif : effet de la darbépoétine alfa sur la réduction de la mortalité, morbidité et qualité de vie chez les patients insuffisants cardiaques chroniques et anémiés. Inclusion : 2600 patients : NYHA classe II-IV, FE < ou = 40% et [Hb] < ou = 12g/dL et > 9g/dL Etude randomisée double-aveugle versus placebo : darbopoétine SC ou Pla Seuil [Hb] : 13g/dL (pas > 14, 5g/dL) Critère d'évaluation primaire : délai jusqu'au décès toute cause ou 1ère hospitalisation pour aggravation de l'insuffisance cardiaque				

Clcr : clairance de la créatinine
GR : globule rouge
[Hb] : concentration en hémoglobine
Hosp: hospitalisation
[Hte] : hématocrite
HTA: hypertension
ICC : insuffisant cardiaque chronique
VO2 : volume d'oxygène expiré en ml/kg/min
KCCQ : Kansas City Cardiomyopathy Questionnaire
FEVG: fraction d'éjection ventriculaire gauche
MLHFQ: Minnesota Living With
NYHA: New York Heart Association
PGA: patient's global assessment of change
Vol Plasm : volume plasmatique
BNP : peptide natriurétique de type B plasmatique
Classe NYHA: New York Heart Association
6MWT : distance parcourue à pied en 6 minutes
VG : ventricule gauche
VD : ventricule droit
Pla : placebo
Creat : creatinine
IL-6 : interleukine

Bibliographie

Les référentiels de la Juste prescription du CEDIT (AP-HP), des Pharmaciens de CHU et des Hospices Civils de Lyon ont été les documents de base du travail bibliographique.

La recherche bibliographique a été réalisée par interrogation systématique des banques de données Medline, Embase et Pascal. Elle a identifié préférentiellement les essais cliniques et les revues de synthèse publiés en langue française ou anglaise après janvier 2000.

1. van der Meer P, Groenveld HF, Januzzi JL Jr, van Veldhuisen DJ.Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. Heart. 2009 Aug;95(16):1309-14.
2. Tehrani F, Dhesi P, Daneshvar D, Phan A, Rafique A, Siegel RJ, Cercek B. Erythropoiesis Stimulating Agents in Heart Failure Patients with Anemia: A Meta-Analysis.Cardiovasc Drugs Ther. 2009 Oct 28.
3. Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, Massie BM, Wasserman SM, Trotman ML, Sun Y, Knusel B, Armstrong P; Study of Anemia in Heart Failure Trial (STAMINA-HeFT) Group. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation. 2008 Jan 29;117(4):526-35.
4. van Veldhuisen DJ, Dickstein K, Cohen-Solal A, Lok DJ, Wasserman SM, Baker N, Rosser D, Cleland JG, Ponikowski P. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. Eur Heart J. 2007 Sep;28(18):2208-16
5.Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymlinski R, Ryan E, Wasserman SM, Baker N, Rosser D, Rosen SD, Poole-Wilson PA, Banasiak W, Coats AJ, McDonald K**.** Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2007 Feb 20;49(7):763-4.
6. Kourea K, Parissis JT, Farmakis D, Panou F, Paraskevaidis I, Venetsanou K, Filippatos G, Kremastinos DT. Effects of darbepoetin-alpha on plasma pro-inflammatory cytokines, anti-inflammatory cytokine interleukin-10 and soluble Fas/Fas ligand system in anemic patients with chronic heart failure. Atherosclerosis. 2008 Jul;199(1):215-21.
7. Kourea K, Parissis JT, Farmakis D, Paraskevaidis I, Panou F, Filippatos G, Kremastinos DT. Effects of darbepoetin-alpha on quality of life and emotional stress in anemic patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2008 Jun;15(3):365-9.
8. Parissis JT, Kourea K, Panou F, Farmakis D, Paraskevaidis I, Ikonomidis I, Filippatos G, Kremastinos DT. Effects of darbepoetin alpha on right and left ventricular systolic and diastolic function in anemic patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy.Am Heart J. 2008 Apr;155(4):751.e1-7.
9. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation. 2003 Jan 21;107(2):294-9
10.Silverberg DS, Wexler D, Blum M, Sheps D, Schwartz D, Yachnin T, Baruch R, Tchebiner J, Zubkov A, Shaked M, Steinbruch S, Keren G, Iaina A. Aggressive therapy of congestive heart failure and associated chronic renal failure with medications and correction of anemia stops or slows the progression of both diseases. Perit Dial Int. 2001;21 Suppl 3:S236-40.
11. Palazzuoli A, Silverberg D, Iovine F, Capobianco S, Giannotti G, Calabrò A, Campagna SM, Nuti R. Erythropoietin improves anemia exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia. Am Heart J. 2006 Dec;152(6):1096.e9-15.
12. Silverberg DS, Wexler D, Blum M, Tchebiner JZ, Sheps D, Keren G, Schwartz D, Baruch R, Yachnin T, Shaked M, Schwartz I, Steinbruch S, Iaina A. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dial Transplant. 2003 Jan;18(1):141-6.
13. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A.The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol. 2001 Jun 1;37(7):1775-80.
14. Silverberg DS, Wexler D, Blum M, Iaina A, Sheps D, Keren G, Scherhag A, Schwartz D. Effects of treatment with epoetin beta on outcomes in patients with anaemia and chronic heart failure. Kidney Blood Press Res. 2005;28(1):41-7.
15. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000 Jun;35(7):1737-44.
16. McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, Polu KR, Solomon SD, Sun Y, Swedberg K, Tendera M, van Veldhuisen DJ, Wasserman SM, Young JB; RED-HF Committees and Investigators. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Fail. 2009 Aug;11(8):795-801.
17. Silverberg DS, Wexler D, Iaina A. The role of anemia in the progression of congestive heart failure. Is there a place for erythropoietin and intravenous iron? J Nephrol. 2004 Nov-Dec;17(6):749-61
18. Cleland JG, Coletta AP, Clark AL, Velavan P, Ingle L. Clinical trials update from the European Society of Cardiology Heart Failure meeting and the American College of Cardiology: darbepoetin alfa study, ECHOS, and ASCOT-BPLA.Eur J Heart Fail. 2005 Aug;7(5):937-9.
19. Silverberg DS, Wexler D, Iaina A, Schwartz D. The role of correction of anaemia in patients with congestive heart failure: a short review. Eur J Heart Fail. 2008 Sep;10(9):819-23.
20. Mak G, Murphy NF, McDonald K. Anemia in heart failure: to treat or not to treat? Curr Treat Options Cardiovasc Med. 2008 Dec;10(6):455-64.
21.Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol. 2008 Aug 12;52(7):501-11.
22. Kremastinos DT. Anaemia in chronic heart failure: is there a rationale to treat?Hellenic J Cardiol. 2007 Jul-Aug;48(4):249-50 : no abstract
23. Murphy NF, McDonald K. Treatment of anaemia in chronic heart failure--optimal approach still unclear.
Eur Heart J. 2007 Sep;28(18):2185-7. Epub 2007 Aug 17 : no abstract
24. van Veldhuisen DJ, McMurray JJ; RED-HF Executive Committee. Are erythropoietin stimulating proteins safe and efficacious in heart failure? Why we need an adequately powered randomised outcome trial.
Eur J Heart Fail. 2007 Feb;9(2):110-2. Epub 2007 Jan 30 : no abstract

van der Meer P, Groenveld HF, Januzzi JL Jr, van Veldhuisen DJ. Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. Heart. 2009 Aug;95(16):1309-14.

BACKGROUND: Anaemia is common in patients with chronic heart failure (HF), and erythropoiesis stimulating proteins (ESPs) are frequently used for its treatment. However, recent studies in patients with malignancies and renal failure have raised concerns about the safety of these agents. OBJECTIVE: To determine whether treatment of anaemic patients with chronic HF with ESPs is associated with an effect on morbidity and mortality. DATA SOURCES: A systematic literature search in Medline, the Cochrane Controlled Trials Register Database and ClinicalTrials.gov through July 2008 was performed. Study selection: Randomised clinical trials comparing the effect of ESP treatment with placebo or usual care in anaemic patients with HF were included. RESULTS: Seven randomised controlled trials were identified that enrolled 650 patients, of whom 363 were treated with ESPs and 287 with placebo. ESP treatment had a significantly lower risk of HF hospitalisation (risk ratio (RR) = 0.59; 95% CI 0.41 to 0.86; p = 0.006).There was no significant difference in the mortality risk between the two groups (RR = 0.69; 95% CI 0.39 to 1.23; p = 0.21). No significant differences were observed in the occurrence of hypertension or venous thrombosis. CONCLUSIONS: In chronic HF, treatment with ESPs is not associated with a higher mortality rate or more adverse events, whereas a beneficial effect on HF hospitalisation is seen. These outcomes are in contrast with studies in cancer and kidney disease, and support a large phase III morbidity and mortality trial of anaemia correction in patients with chronic HF.

Tehrani F, Dhesi P, Daneshvar D, Phan A, Rafique A, Siegel RJ, Cercek B. Erythropoiesis Stimulating Agents in Heart Failure Patients with Anemia: A Meta-Analysis.Cardiovasc Drugs Ther. 2009 Oct 28.

BACKGROUND: Anemia is prevalent in patients with heart failure and an independent prognostic sign of poor outcome. The current report is a meta-analysis of published clinical trials assessing the use of erythropoeisis stimulating agents (ESA) in heart failure (HF) patients with anemia. METHODS: Literature and Medline search was performed to identify studies with control groups (case-control, cohort or randomized controlled trials) that examined the effect of ESA therapy in patients with HF and anemia. RESULTS: Seven prospective controlled trials met inclusion criteria (n = 663 subjects). The ESA studied was darbepoetin in 4 trials and erythropoietin in 3 trials. Mean follow up period ranged from 12 to 27 weeks. Compared to placebo ESA therapy was associated with improvement in six cardiovascular parameters assessed by at least three of the analyzed trials, including increase in hemoglobin levels 2.35(95% confidence interval [CI], 1.76-2.93, P < 0.00001), increase in exercise duration 0.91(95% CI, 0.08-1.73, P = 0.03), improvement in New York Heart Association functional class -1.46(95% CI, -2.32 to -0.60, P = 0.0009), improvement in 6-minute walk test 1.42(95% CI, 0.31-2.54, P = 0.01), decrease in B-type natriuretic peptide -0.54(95% CI, -1.03 to -0.06, P = 0.03), and improvement in peak oxygen consumption 0.93(95% CI, 0.52-1.34, P < 0.00001). CONCLUSION: In patients with heart failure and anemia, erythropoiesis stimulating agent therapy appears to have a positive effect on several important cardiovascular parameters, compared to control therapy. Large prospective randomized controlled trials are warranted to comprehensively evaluate the potential effects of erythropoiesis stimulating agents on clinical outcomes in heart failure patients with anemia.

Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, Massie BM, Wasserman SM, Trotman ML, Sun Y, Knusel B, Armstrong P; Study of Anemia in Heart Failure Trial (STAMINA-HeFT) Group. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation. 2008 Jan 29;117(4):526-35.

BACKGROUND: Substantial evidence suggests that anemia is an independent risk factor for worse outcomes in patients with heart failure (HF). The Study of Anemia in Heart Failure Trial (STAMINA-HeFT) is the largest multicenter, randomized, double-blind, placebo-controlled trial to date evaluating the effect of treating anemia in HF. METHODS AND RESULTS: Patients (N=319) with symptomatic HF, left ventricular ejection fraction < or = 40%, and hemoglobin > or = 9.0 g/dL and < or = 12.5 g/dL were randomized (double-blind) to placebo (N=157) or darbepoetin alfa (N=162) subcutaneously every 2 weeks for 1 year (target hemoglobin, 14.0+/-1.0 g/dL). The primary end point was change from baseline to week 27 in treadmill exercise time. Secondary end points were change from baseline in New York Heart Association class and quality of life at week 27. An additional prespecified efficacy analysis included the time to death by any cause or first HF-related hospitalization by 1 year. At baseline, the median (interquartile range) hemoglobin was 11.4 (10.9, 12.0) g/dL. At week 27, darbepoetin alfa treatment increased median (interquartile range) hemoglobin by 1.8 (1.1, 2.5) g/dL (placebo, 0.3 [-0.2, 1.0] g/dL; P<0.001). Of the patients treated with darbepoetin alfa, 85% achieved 2 consecutive hemoglobin levels of 14.0+/-1.0 g/dL during the study and experienced a hemoglobin increase of > or = 1.0 g/dL from baseline. By intent-to-treat analysis, darbepoetin alfa treatment did not significantly improve exercise duration, New York Heart Association class, or quality of life score compared with placebo. A nonsignificant trend was observed toward a lower risk of all-cause mortality or first HF hospitalization in darbepoetin alfa-treated patients compared with placebo (hazard ratio, 0.68; 95% CI, 0.43, 1.08; P=0.10). Occurrences of adverse events were similar in both treatment groups. CONCLUSIONS: In this study of patients with symptomatic HF and anemia, treatment with

darbepoetin alfa was not associated with significant clinical benefits. Darbepoetin alfa treatment was well tolerated and effectively raised hemoglobin. A trend of lower risk of morbidity and mortality was observed.

---

van Veldhuisen DJ, Dickstein K, Cohen-Solal A, Lok DJ, Wasserman SM, Baker N, Rosser D, Cleland JG, Ponikowski P. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. Eur Heart J. 2007 Sep;28(18):2208-16

AIMS: Anaemia is common in chronic heart failure (CHF) and associated with worse outcome. This randomized, double-blind, placebo-controlled study evaluated the effect of two darbepoetin alfa dosing regimens on haemoglobin (Hb) rate of rise and clinical effects in patients with CHF and anaemia. METHODS AND RESULTS: Patients with CHF (>or=3 months), left ventricular ejection fraction (LVEF) <or= 40%, and Hb 9.0 to 12.5 g/dL received darbepoetin alfa subcutaneously every 2 weeks for 26 weeks at a starting weight-adjusted dose of 0.75 mcg/kg (n = 56) or a fixed dose of 50 mcg (n = 54), or placebo (n = 55), to gradually achieve and maintain a target Hb of 14.0 +/- 1.0 g/dL. Endpoints included rate of Hb rise per week during titration, safety, and changes in 6 min walk distance, New York Heart Association (NYHA) class, LVEF, and quality of life. Most subjects were NYHA class II-III. Mean (SD) age was 71 (11) years, LVEF was 28 (9), and Hb 11.5 (0.7) g/dL. Rate of Hb rise was equivalent between darbepoetin alfa weight-based (+1.87 +/- 1.36 g/dL) and fixed dosing (+1.64 +/- 0.98 g/dL) groups, vs. + 0.07 +/- 1.08 g/dL in the placebo group. Mean Hb concentrations by week 27 were 13.4 and 13.2 g/dL, in the weight-based and fixed dosing groups, respectively. There were non-significant improvements in the combined darbepoetin alfa group vs. placebo for 6 min walk distance (P = 0.074) and Patient's Global Assessment score (P = 0.057). There was a significant improvement in Kansas City Cardiomyopathy Questionnaire total symptom score (8.2 vs. 1.5 points; P = 0.027) but no change in NYHA class, LVEF, and Minnesota Living With Heart Failure Questionnaire score. Six treatment-unrelated deaths occurred in the 110 darbepoetin alfa treated patients, and none in the 55 placebo treated patients. Other adverse events were similar between groups. CONCLUSION: In this study of patients with CHF and anaemia, treatment with darbepoetin alfa raised Hb using different dosing regimens. Darbepoetin alfa improved some quality of life indices, but its safety requires further exploration. Larger trials are needed to determine the effects on long-term morbidity and mortality.

Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymlinski R, Ryan E, Wasserman SM, Baker N, Rosser D, Rosen SD, Poole-Wilson PA, Banasiak W, Coats AJ, McDonald K**.** Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2007 Feb 20;49(7):763-4.

OBJECTIVES: This study sought to investigate whether darbepoetin alfa, an erythropoiesis-stimulating protein (ESP), improves exercise capacity in patients with symptomatic chronic heart failure (CHF) and anemia. BACKGROUND: Anemia is common in patients with CHF. METHODS: In a multicenter, randomized, double-blind, placebo-controlled study, CHF patients with anemia (hemoglobin > or =9.0 to < or =12.0 g/dl) received subcutaneous placebo (n = 22) or darbepoetin alfa (n = 19) at a starting dose of 0.75 microg/kg every 2 weeks for 26 weeks. The primary end point was change in exercise tolerance from baseline to week 27 as measured by peak oxygen uptake (ml/min/kg body weight). Other end points included changes in absolute peak VO2 (ml/min), exercise duration, and health-related quality of life. RESULTS: Differences (95% confidence interval) in mean changes from baseline to week 27 between treatment groups were 1.5 g/dl (0.5 to 2.4) for hemoglobin concentration (p = 0.005), 0.5 ml/kg/min (-0.7 to 1.7) for peak VO2 (p = 0.40), 45 ml/min (-35 to 127) for absolute peak VO2 (p = 0.27), and 108 s (-11 to 228) for exercise duration (p = 0.075). Patients receiving darbepoetin alfa compared with placebo had an improvement in self-reported Patient's Global Assessment of Change (79% vs. 41%, p = 0.01) but no significant differences in the Kansas City Cardiomyopathy and Minnesota Living with Heart Failure Questionnaire scores. Darbepoetin alfa was well tolerated. CONCLUSIONS: In patients with symptomatic CHF and anemia, darbepoetin alfa increased and maintained hemoglobin concentrations and improved health-related quality of life. A trend toward increased exercise time but not peak VO2 was observed.

Kourea K, Parissis JT, Farmakis D, Panou F, Paraskevaidis I, Venetsanou K, Filippatos G, Kremastinos DT. Effects of darbepoetin-alpha on plasma pro-inflammatory cytokines, anti-inflammatory cytokine interleukin-10 and soluble Fas/Fas ligand system in anemic patients with chronic heart failure. Atherosclerosis. 2008 Jul;199(1):215-21.

Pro-inflammatory cytokine over-expression may be implicated to the pathogenesis of anemia in chronic heart failure (CHF) through the suppression of bone marrow erythropoiesis. Erythropoietin administration has anti-inflammatory and anti-apoptotic properties in experimental CHF models and improves exercise capacity in anemic CHF patients. The present study investigates the effects of recombinant human erythropoietin analogue darbepoetin-alpha on circulating pro-inflammatory cytokines and soluble Fas/soluble Fas ligand system in patients with CHF and anemia. Forty-one CHF patients (NYHA class: II-III; left ventricular (LV) ejection fraction (EF) <40%; hemoglobin <12.5g/dl; serum creatinine <2.5mg/dl) were randomized to receive either 3-month darbepoietin-* at 1.5 microg/kg every 20 days plus iron orally (n=21) or placebo plus iron orally (n=20). LV systolic function, plasma B-type natriuretic peptide (BNP), inflammatory markers (TNF-*, IL-6, CRP), anti-inflammatory cytokine IL-10, endothelial adhesion molecules (soluble ICAM-1 and VCAM-1) and soluble apoptosis mediators

(soluble Fas, soluble Fas ligand), and 6-min walking distance were assessed at baseline and 3 months post-treatment. In darbepoetin-* treated patients, plasma BNP (451 (62-2770) from 802 (476-4440) pg/ml, p=0.002), IL-6 (6.5+/-4.7 from 10.5+/-7.8 pg/ml, p=0.013) and soluble Fas ligand (53.2+/-16.6 from 59.2+/-17.9 pg/ml, p=0.023) decreased significantly, while LVEF (32+/-6 from 26+/-6%, p<0.001), hemoglobin (12.8+/-1.4 from 10.9+/-1.0 g/dl, p<0.001) and 6-min walked distance (274+/-97 from 201+/-113m, p<0.01) increased significantly. No significant changes were observed in the placebo arm, except for a worsening in 6-min walked distance (p=0.044). In conclusion, darbepoetin-alpha reduces circulating pro-inflammatory cytokine IL-6 and apoptotic mediator soluble Fas ligand in CHF patients with anemia, with a parallel improvement of cardiac performance and exercise capacity.

Kourea K, Parissis JT, Farmakis D, Paraskevaidis I, Panou F, Filippatos G, Kremastinos DT. Effects of darbepoetin-alpha on quality of life and emotional stress in anemic patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2008 Jun;15(3):365-9.

OBJECTIVE: Anemia is a frequent comorbidity in chronic heart failure (CHF) adversely affecting patients' prognosis. Erythropoietin seems to improve exercise capacity in CHF patients. This study investigates the effects of recombinant human erythropoietin analog darbepoetin-alpha on quality of life and emotional stress, evaluated by relevant questionnaires in patients with CHF and anemia. METHODS: Forty-one CHF patients [New York Heart Association class: II-III; left ventricular (LV) ejection fraction (EF)<40%; hemoglobin<12.5 g/dl; serum creatinine<2.5 mg/dl] were randomized (1:1) to receive either 3-month darbepoietin-alpha at 1.5 microg/Kg every 20 days plus iron orally (n=21) or placebo plus iron orally (n=20). Echocardiographic LVEF, questionnaires addressing quality of life (Kansas City Cardiomyopathy Questionnaire, functional and overall, Duke's Activity Status Index) and emotional stress [Zung self-rating depression scale (SDS), Beck Depression Inventory], as well as plasma b-type natriuretic peptide and 6-min walking distance (6MWT as a marker of exercise capacity) were assessed at baseline and posttreatment. RESULTS: A significant improvement in LVEF (32+/-6 from 26+/-6%, P<0.001), 6MWT (274+/-97 from 201+/-113 m, P<0.01), hemoglobin (12.8+/-1.4 from 10.9+/-1.0 g/dl, P<0.001) and plasma b-type natriuretic peptide (517+/-579 from 829+/-858 pg/ml, P=0.002) was observed posttreatment only in darbepoetin-treated group. Kansas City Cardiomyopathy Questionnaire functional (78+/-14 from 57+/-24%, P<0.01) and overall (68+/-20 from 47+/-22, P<0.001), Duke's Activity Status Index (19+/-11 from 14+/-9, P<0.05), Zung SDS (38+/-10 from 47+/-11, P<0.05) and Beck Depression Inventory (11+/-9 from 16+/-10, P<0.05) scores also improved in darbepoetin-treated patients, whereas they remain unchanged in the placebo group except for the Zung SDS which worsened (P<0.05). A significant correlation between drug-induced percent changes in 6MWT and Zung SDS (r=-0.627, P<0.05) was also observed. CONCLUSIONS: Darbepoetin-alpha improves quality of life and emotional stress in CHF patients with anemia, with a parallel increase in exercise capacity.

Parissis JT, Kourea K, Panou F, Farmakis D, Paraskevaidis I, Ikonomidis I, Filippatos G, Kremastinos DT. Effects of darbepoetin alpha on right and left ventricular systolic and diastolic function in anemic patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy.Am Heart J. 2008 Apr;155(4):751.e1-7.

BACKGROUND: Anemia is a frequent condition in chronic heart failure (CHF) that affects adversely long-term cardiac outcomes. We sought to investigate the effects of recombinant human erythropoietin analogue darbepoetin alpha on left (LV) and right ventricular (RV) function and neurohormonal activation in patients with CHF and anemia. METHODS: Thirty-two CHF patients (New York Heart Association class II-III, LV ejection fraction [EF] <40%, hemoglobin level <12.5 g/dL, serum creatinine level <2.5 mg/dL) were randomized (2:1) to receive either a 3-month darbepoetin alpha regimen at 1.5 microg/kg every 20 days plus oral iron (n = 21) or placebo plus oral iron (n = 11). Echocardiographic indices of LV systolic and diastolic function and RV function, plasma B-type natriuretic peptide (BNP) and 6-minute walked distance were assessed at baseline and posttreatment. RESULTS: Regarding LV function, only treatment with darbepoetin alpha caused a significant improvement in LVEF (F = 22.001, P < .001), end-systolic wall stress (F = 4.934, P = .034), mitral annulus systolic displacement (F = 6.710, P < .015), isovolumic relaxation time (F = 4.909, P = .035), and E/e ratio (F = 7.833, P = .009). The RV systolic pressure (F = 7.715, P = .009) as well as tricuspid annulus systolic displacement and RVEF (F = 9.264, P = .005) were significantly improved only in the darbepoetin alpha group. Darbepoetin alpha had also alpha beneficial effect on New York Heart Association class (F = 14.586, P = .001), plasma BNP (F = 14.781, P = .001), and 6-minute walk test (F = 19.926, P < .001), whereas these parameters did not significantly change in the placebo-treated patients. CONCLUSION: Darbepoetin alpha improves both LV and RV performance and exercise capacity and counteracts neurohormonal activation in CHF patients with anemia. The drug effects on LV diastolic function, RV function, and LV end-systolic wall stress, in particular, are novel findings, with a potential important contribution to patients' symptomatic improvement.

Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation. 2003 Jan 21;107(2):294-9

BACKGROUND: Patients with chronic heart failure (CHF) are frequently anemic. An increase in hemoglobin could enhance exercise performance by increasing oxygen delivery. We investigated the effect of erythropoietin (EPO)

on exercise performance in anemic patients with CHF. METHODS AND RESULTS: Twenty-six anemic patients aged 57+/-11 years were randomized to receive EPO (15 000 to 30 000 IU per week) or placebo for 3 months. Parameters measured at baseline and end therapy included blood parameters (hemoglobin, hematocrit, plasma volume), exercise parameters (peak oxygen consumption [VO2], exercise duration, 6-minute walk), muscle aerobic metabolism (half-time of VO2 and near infrared recovery), and forearm vasodilatory function. EPO was well tolerated by all patients. Twelve patients in the EPO group felt improvement versus 1 in the placebo group (P<0.05). There were significant increases in hemoglobin (11.0+/-0.5 to 14.3+/-1.0 g/dL, P<0.05), peak VO2 (11.0+/-1.8 to 12.7+/-2.8 mL. min(-1) x kg(-1), P<0.05) and exercise duration (590+/-107 to 657+/-119 s, P<0.004) in the EPO group but no significant changes in the control group. Resting and hyperemic forearm vascular resistance and indices of the rate of muscle oxidative capacity were unchanged in both groups. CONCLUSION: EPO significantly enhances exercise capacity in patients with CHF. One mechanism of improvement in VO2 is increased oxygen delivery from increased hemoglobin concentration.

Palazzuoli A, Silverberg D, Iovine F, Capobianco S, Giannotti G, Calabrò A, Campagna SM, Nuti R. Erythropoietin improves anemia exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia. Am Heart J. 2006 Dec;152(6):1096.e9-15.
BACKGROUND: Anemia is now recognized as being a common finding in CHF and is associated with increased mortality and morbidity. However, it is uncertain whether the anemia is actually causing the worse prognosis or is merely a marker of more severe cardiac disease. Previous intervention studies with subcutaneous (s.c.) beta-EPO in combination with iron have either been uncontrolled or case-controlled studies. We report a randomized, double-blind, placebo-controlled study of the combination of s.c. EPO and oral iron versus oral iron alone in patients with anemia and resistant CHF. OBJECTIVES: The present study examines, in patients with advanced congestive heart failure (CHF) and anemia, the effects of beta-erythropoietin (EPO) and oral iron on the anemia and on cardiac and renal functional parameters. METHODS: Forty consecutive subjects with moderate to severe CHF and anemia (hemoglobin [Hb] <11 g/dL) were studied. They were randomized to receive, in a double-blind fashion, either (a) (group A, the treatment group, 20 patients) s.c. beta-EPO for 3 months twice weekly, in addition to daily oral iron, or (b) (group B, the placebo group, 20 patients) normal saline in s.c. injections and daily oral iron. Two patients in group B were eventually excluded because of a fall of Hb <8 g/dL requiring transfusion, leaving 18 patients in group B. After the 3-months study, the group A patients were maintained on the same treatment for an additional 9 months, whereas in Group B, the placebo and oral iron were stopped. RESULTS: In group A, after a mean of 3.5 +/- 0.8 months of treatment, there was a significant increase in Hb from 10.4 +/- 0.6 to 12.4 +/- 0.8 g/dL (P < .01); a significant improvement in New York Heart Association functional class from 3.5 +/- 0.6 to 2.8 +/- 0.5 (P < .05); a longer endurance time on exercise testing, from 5.8 +/- 2.2 to 7.8 +/- 2.5 minutes (P < .01); a greater distance walked on exercise testing, from 278 +/- 55 to 356 +/- 88 meters (P < .01); a significant increase in the peak oxygen consumption (VO2) from 12.8 +/- 2.8 to 15.1 +/- 2.8 mL/kg per minute (<.05); and the VO2 at the anaerobic threshold, from 9.2 +/- 2.0 to 13.2 +/- 3.6 mL/kg minute (P < .01). There was also a significant fall in plasma B-type natriuretic peptide levels from 568 +/- 320 to 271 +/- 120 pg/mL (P < .01), a significant reduction in serum creatinine (P < .01), and an increase in estimated creatinine clearance (P < .05). In group B, there were no significant changes in any of the above parameters over the study period. At the end of the 1-year study, the Hb was still higher in group A than group B, and the rate of hospital admissions/patients over the year averaged 0.8 +/- 0.2 in group A and 1.7 +/- 0.8 in group B (P < .01). CONCLUSIONS: In anemic CHF patients, correction of anemia with EPO and oral iron leads to improvement in New York Heart Association status, measured exercise endurance, oxygen use during exercise, renal function and plasma B-type natriuretic peptide levels and reduces the need for hospitalization.

Silverberg DS, Wexler D, Blum M, Sheps D, Schwartz D, Yachnin T, Baruch R, Tchebiner J, Zubkov A, Shaked M, Steinbruch S, Keren G, Iaina A. Aggressive therapy of congestive heart failure and associated chronic renal failure with medications and correction of anemia stops or slows the progression of both diseases. Perit Dial Int. 2001;21 Suppl 3:S236-40.

The prevalence of congestive heart failure (CHF) is increasing rapidly in the community. We and others have shown that the prevalence and severity of both anemia and chronic renal failure (CRF) increase steadily with increasing severity of CHF. We have also shown that CHF patients may be resistant to standard drug therapy for CHF as long as the associated anemia is not corrected, and that correction of the anemia with subcutaneous erythropoietin and intravenous iron sucrose (Venofer: Vifor International, St. Gallen, Switzerland) may improve both the CHF and CRF and markedly reduce hospitalizations without causing side effects. We report here our experience with correcting anemia in this manner in 126 cases of anemic-resistant CHF patients. As in our previous studies, correction of the anemia improved both CHF and CRF, and reduced hospitalizations. Our studies suggest that correction of even mild anemia in CHF may be an important addition to the treatment of patients with the combination of CHF and CRF.

Silverberg DS, Wexler D, Blum M, Tchebiner JZ, Sheps D, Keren G, Schwartz D, Baruch R, Yachnin T, Shaked M, Schwartz I, Steinbruch S, Iaina A. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dial Transplant. 2003 Jan;18(1):141-6.

BACKGROUND: A mild anaemia is often found in patients with congestive heart failure (CHF), but its significance is uncertain. In an open uncontrolled study we investigated the effect of correcting this anaemia [haemoglobin (Hb) 9.5-11.5 g%] with subcutaneous (s.c.) erythropoietin (Epo) and intravenous (i.v.) iron (Fe) in 179 patients, 84 type II diabetics and 95 non-diabetics, with moderate to severe CHF which was resistant to maximally tolerated doses of standard CHF medications. METHODS: EPO, s.c., was given every 1-3 weeks to achieve and maintain the Hb at 12.5 g%. Fe (Fe sucrose-Venofer) was added i.v. as necessary to maintain the Fe stores. Duration of treatment was 11.8 + 8.2 months. RESULTS: With the Epo-Fe treatment the Hb increased from 10.41 +/- 1.0 to 13.1 +/- 1.3 g% in diabetics and from 10.5 +/- 1.0 to 12.9 +/- 1.2 g% in non-diabetics. Comparing the diabetics and non-diabetics, the New York Heart Association functional class improved by 34.8 and 32.4%, respectively. breathlessness and/or fatigue, as measured by a self-administered Visual Analogue Scale, improved by 69.7 and 67.4%, and the left ventricular ejection fraction improved by 7.4 and 11.5%, respectively. The number of hospitalizations fell by 96.4 and 95.3%, respectively, compared with the pre-treatment period. Although the glomerular filtration rate (GFR) was falling at a rate of approximately 1 ml/min/month before the study in both groups, neither the mean serum creatinine nor the GFR changed significantly during the study period. The mean dose of Epo needed, measured in IU/week/kg body weight, was similar in the two groups. CONCLUSION: The correction of the mild anaemia that was found in diabetics and non-diabetics with resistant CHF and mild to moderate chronic renal failure improved the cardiac function and patient functional status, stabilized the renal function and markedly reduced the need for hospitalization.

Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A.The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol. 2001 Jun 1;37(7):1775-80.

OBJECTIVES: This is a randomized controlled study of anemic patients with severe congestive heart failure (CHF) to assess the effect of correction of the anemia on cardiac and renal function and hospitalization. BACKGROUND: Although mild anemia occurs frequently in patients with CHF, there is very little information about the effect of correcting it with erythropoietin (EPO) and intravenous iron. METHODS: Thirty-two patients with moderate to severe CHF (New York Heart Association [NYHA] class III to IV) who had a left ventricular ejection fraction (LVEF) of < or =40% despite maximally tolerated doses of CHF medications and whose hemoglobin (Hb) levels were persistently between 10.0 and 11.5 g% were randomized into two groups. Group A (16 patients) received subcutaneous EPO and IV iron to increase the level of Hb to at least 12.5 g%. In Group B (16 patients) the anemia was not treated. The doses of all the CHF medications were maintained at the maximally tolerated levels except for oral and intravenous (IV) furosemide, whose doses were increased or decreased according to the clinical need. RESULTS: Over a mean of 8.2+/-2.6 months, four patients in Group B and none in Group A died of CHF-related illnesses. The mean NYHA class improved by 42.1% in A and worsened by 11.4% in B. The LVEF increased by 5.5% in A and decreased by 5.4% in B. The serum creatinine did not change in A and increased by 28.6% in B. The need for oral and IV furosemide decreased by 51.3% and 91.3% respectively in A and increased by 28.5% and 28.0% respectively in B. The number of days spent in hospital compared with the same period of time before entering the study decreased by 79.0% in A and increased by 57.6% in B. CONCLUSIONS: When anemia in CHF is treated with EPO and IV iron, a marked improvement in cardiac and patient function is seen, associated with less hospitalization and renal impairment and less need for diuretics.

Silverberg DS, Wexler D, Blum M, Iaina A, Sheps D, Keren G, Scherhag A, Schwartz D. Effects of treatment with epoetin beta on outcomes in patients with anaemia and chronic heart failure. Kidney Blood Press Res. 2005;28(1):41-7.

Anaemia is frequently found in patients with chronic heart failure (CHF) and has been associated with an increase in mortality and morbidity, impaired cardiac and renal function and a reduced quality of life (QoL) compared with non-anaemic CHF patients. Correction of anaemia with recombinant human erythropoietin (epoetin) has been associated with an improvement in CHF in both controlled and uncontrolled studies. The present study describes our findings in a series of 78 consecutive patients with symptomatic CHF and anaemia (haemoglobin (Hb) level <12.0 g/dl) treated with epoetin beta and, if necessary, intravenous iron sucrose. Over a mean observation period of 20.7 +/- 12.1 months, mean Hb levels increased from 10.2 +/- 1.1 to 13.5 +/- 1.2 g/dl, $p < 0.01$. New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) were significantly improved and the number of hospitalizations was significantly reduced with the period before treatment (all $p < 0.01$). Serum creatinine and creatinine clearance (CCr) were 2.2 +/- 0.9 mg/dl and 32.5 +/- 26.5 ml/min, respectively, at baseline, and remained stable over the observation period. Interestingly, >90% of the patients had concomitant mild-to-moderate chronic kidney disease at baseline and study end (CKD), as defined by the accepted diagnostic criterion of a CCr <60 ml/min. CONCLUSIONS: The correction of the anaemia with epoetin beta together with initial intravenous iron supplementation, resulted in significant improvements in NYHA class and cardiac function, and a reduction in hospitalization rate. Moreover, renal function was maintained stable in most patients.

Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol. 2000 Jun;35(7):1737-44.

OBJECTIVES: This study evaluated the prevalence and severity of anemia in patients with congestive heart failure (CHF) and the effect of its correction on cardiac and renal function and hospitalization. BACKGROUND: The prevalence and significance of mild anemia in patients with CHF is uncertain, and the role of erythropoietin with intravenous iron supplementation in treating this anemia is unknown. METHODS: In a retrospective study, the records of the 142 patients in our CHF clinic were reviewed to find the prevalence and severity of anemia (hemoglobin [Hb] <12 g). In an intervention study, 26 of these patients, despite maximally tolerated therapy of CHF for at least six months, still had had severe CHF and were also anemic. They were treated with subcutaneous erythropoietin and intravenous iron sufficient to increase the Hb to 12 g%. The doses of the CHF medications, except for diuretics, were not changed during the intervention period. RESULTS: The prevalence of anemia in the 142 patients increased with the severity of CHF, reaching 79.1% in those with New York Heart Association class IV. In the intervention study, the anemia of the 26 patients was treated for a mean of 7.2 +/- 5.5 months. The mean Hb level and mean left ventricular ejection fraction increased significantly. The mean number of hospitalizations fell by 91.9% compared with a similar period before the study. The New York Heart Association class fell significantly, as did the doses of oral and intravenous furosemide. The rate of fall of the glomerular filtration rate slowed with the treatment. CONCLUSIONS: Anemia is very common in CHF and its successful treatment is associated with a significant improvement in cardiac function, functional class, renal function and in a marked fall in the need for diuretics and hospitalization.

McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, Polu KR, Solomon SD, Sun Y, Swedberg K, Tendera M, van Veldhuisen DJ, Wasserman SM, Young JB; RED-HF Committees and Investigators. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Fail. 2009 Aug;11(8):795-801.

BACKGROUND: Patients with heart failure (HF) and anaemia have greater functional impairment, worse symptoms, increased rates of hospital admission, and a higher risk of death, compared with non-anaemic HF patients. Whether correcting anaemia can improve outcomes is unknown. OBJECTIVE: The Reduction of Events with Darbepoetin alfa in Heart Failure trial (RED-HF; Clinical Trials.gov NCT 003 58215) was designed to evaluate the effect of the long-acting erythropoietin-stimulating agent darbepoetin alfa on mortality and morbidity (and quality of life) in patients with HF and anaemia. METHODS: Approximately 2600 patients with New York Heart Association class II-IV, an ejection fraction < or =40%, and a haemoglobin (Hb) consistently < or =12.0 g/dL but > or =9.0 g/dL will be enrolled. Patients are randomized 1:1 to double-blind subcutaneous administration of darbepoetin alfa or placebo. Investigators are also blinded to Hb measurements and darbepoetin alfa is dosed to achieve an Hb concentration of 13.0 g/dL (but not exceeding 14.5 g/dL) with sham adjustments of the dose of placebo. The primary endpoint is the time to death from any cause or first hospital admission for worsening HF, whichever occurs first. The study will complete when approximately 1150 subjects experience a primary endpoint.

Silverberg DS, Wexler D, Iaina A. The role of anemia in the progression of congestive heart failure. Is there a place for erythropoietin and intravenous iron? J Nephrol. 2004 Nov-Dec;17(6):749-61

Anemia is found in about one-third of all cases of congestive heart failure (CHF). The most likely common cause is chronic kidney insufficiency (CKI), which is present in about half of all CHF cases. The CKI is likely to be due to the renal vasoconstriction that often accompanies CHF and can cause long-standing renal ischemia. This reduces the amount of erythropoietin (EPO) produced in the kidney and leads to anemia. However, anemia can occur in CHF without CKI and is likely to be due to excessive cytokine production (for example, tumor necrosis factor-alfa (TNF-alfa) and interleukin-6 (IL-6)), which is common in CHF and can cause reduced EPO secretion, interference with EPO activity in the bone marrow and reduced iron supply to the bone marrow. The anemia itself can worsen cardiac function, both because it causes cardiac stress through tachycardia and increased stroke volume, and because it can cause a reduced renal blood flow and fluid retention, adding further stress to the heart. Long-standing anemia of any cause can cause left ventricular hypertrophy (LVH), which can lead to cardiac cell death through apoptosis and worsen the CHF. Therefore, a vicious circle is set up wherein CHF causes anemia, and the anemia causes more CHF and both damage the kidneys worsening the anemia and the CHF further. We have termed this vicious circle the cardio renal anemia (CRA) syndrome. Patients with CHF who are anemic are often resistant to all CHF medications resulting in being hospitalized repeatedly. Many studies also demonstrate that these patients die more rapidly than their non-anemic counterparts do. In addition, they have a more rapid deterioration in their renal function and can end up on dialysis. There is now evidence from both uncontrolled and controlled studies that early correction of the CHF anemia with subcutaneous EPO and intravenous (i.v.) iron improves shortness of breath and fatigue, cardiac function, renal function and exercise capability, dramatically reducing the need for hospitalization. For these reasons, it is not surprising that quality of life has also been shown to improve. As both CHF and end-stage renal disease (ESRD) are rapidly increasing, the possibility that

these twin conditions can be improved by the adequate treatment of anemia offers new hope for slowing the progression of both conditions.

Cleland JG, Coletta AP, Clark AL, Velavan P, Ingle L. Clinical trials update from the European Society of Cardiology Heart Failure meeting and the American College of Cardiology: darbepoetin alfa study, ECHOS, and ASCOT-BPLA.Eur J Heart Fail. 2005 Aug;7(5):937-9.

This article provides information and a commentary on landmark trials presented at the European Society of Cardiology Heart Failure meeting held in June 2005, relevant to the pathophysiology, prevention and treatment of heart failure. All reports should be considered as preliminary data, as analyses may change in the final publication. The erythropoiesis stimulating protein, darbepoetin alfa, increased haemoglobin levels, improved quality of life and showed a trend for improved exercise duration in anaemic patients with symptomatic chronic heart failure. In the ECHOS study, the selective dopamine agonist nolomirole (CHF1035) showed no benefit in heart failure patients. Preliminary results of the ASCOT-BPLA study, which were reported at the American College of Cardiology meeting in March 2005, showed that in hypertensive patients, treatment with a calcium antagonist plus an ACE inhibitor was more effective at reducing cardiovascular outcomes than atenolol plus a diuretic.

Silverberg DS, Wexler D, Iaina A, Schwartz D. The role of correction of anaemia in patients with congestive heart failure: a short review. Eur J Heart Fail. 2008 Sep;10(9):819-23.

Many patients with Congestive Heart Failure (CHF) are anaemic. This anaemia is associated with more severe CHF and a higher incidence of mortality, hospitalisation and morbidity. The only way to prove that the anaemia is causing this worsening of CHF is to correct it. We review here some of the published papers about correction of anaemia. Many studies show a positive effect of Erythropoietin (EPO) or its' derivatives when administered in combination with oral or IV iron, with improvements in left and right ventricular systolic and diastolic function, dilation and hypertrophy and renal function. In addition, a reduction in hospitalisations, diuretic dose, pulmonary artery pressure, plasma volume, heart rate, serum Brain Natriuretic Peptide levels, the inflammatory marker Interleukin 6, soluble Fas ligand--a mediator of apoptosis, and improvements in New York Heart Association class, exercise capacity, oxygen utilization, caloric intake, Quality of Life and the activity of Endothelial Progenitor Cells, have been observed. Iron deficiency may also play an important role in this anaemia, since improvements in CHF have also been reported following treatment with IV iron alone. However, until the ongoing large placebo-controlled studies of the EPO derivative darbepoetin or IV iron are completed, we will not know whether these treatments really influence CHF outcome.

Mak G, Murphy NF, McDonald K. Anemia in heart failure: to treat or not to treat? Curr Treat Options Cardiovasc Med. 2008 Dec;10(6):455-64.

Anemia is a prevalent comorbidity in chronic heart failure (CHF). As studies have demonstrated close links between anemia and a poorer prognosis, there has been an interest in developing treatment strategies for this condition. Anemia is closely associated with disease severity and may be secondary to multiple modifiable causes; therefore, the initial strategies should always include a thorough search for etiology and should focus on optimizing heart failure treatment. Recently, more specific therapies have been assessed, namely erythropoiesis-stimulating agents and iron supplementation therapy. Studies evaluating erythropoietin in heart failure have demonstrated conflicting results to date, with smaller, single-center studies seeming to show a clinical benefit and larger, multicenter trials demonstrating no significant effect on clinical outcome aside from improvement in selected quality-of-life indices. Similarly, studies evaluating iron therapy alone in anemic patients with heart failure have so far shown promising results with regard to clinical and quality-of-life outcomes, but these studies are limited in that they involved small patient numbers. Ongoing studies such as the Reduction of Events with Darbepoetin Alfa in Heart Failure (RED-HF), Iron Supplementation in Heart Failure Patients With Anemia (IRON-HF), and Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF) trials will determine the value of darbepoetin alfa and intravenous iron replacement therapy in anemic CHF patients.

Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol. 2008 Aug 12;52(7):501-11.

Anemia is a common comorbidity in patients with heart failure and is associated with worse long-term outcomes. Although the cause of anemia in heart failure is unclear, the weight of evidence suggests that renal dysfunction, along with neurohormonal and proinflammatory cytokine activation in heart failure, favors the development of anemia of chronic disease, with defective iron utilization, inappropriate erythropoietin production, and depressed bone marrow function. Similarly, the mechanisms by which anemia worsens heart failure outcomes are unknown but may be related to increased myocardial workload. If anemia is a mediator and not just a marker of poor outcomes, correcting anemia could become an important and novel therapeutic target to improve long-term outcomes in such patients. Indeed, several small-sized studies have shown the beneficial effects of empirically

treating anemia in heart failure patients with recombinant erythropoietin and intravenous iron. However, the ideal threshold at which therapy should be initiated and the extent of correction considered safe and desirable in the individual patient with heart failure need to be known. These issues become more important because of increasing safety concerns that recombinant erythropoietin therapy for treating anemia may be associated with adverse cardiovascular outcomes in patients with chronic kidney disease and may worsen cancer in patients receiving chemotherapy to treat various types of cancer. Therefore, further prospectively designed studies are required to address some of these questions. Fortunately, 2 large mortality morbidity trials, TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) in patients with chronic kidney disease and RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) in heart failure patients, are in progress and are likely to provide definitive answers.

Kremastinos DT. Anaemia in chronic heart failure: is there a rationale to treat?
Hellenic J Cardiol. 2007 Jul-Aug;48(4):249-50 : no abstract

Murphy NF, McDonald K. Treatment of anaemia in chronic heart failure--optimal approach still unclear.
Eur Heart J. 2007 Sep;28(18):2185-7. Epub 2007 Aug 17 : no abstract

---

van Veldhuisen DJ, McMurray JJ; RED-HF Executive Committee. Are erythropoietin stimulating proteins safe and efficacious in heart failure? Why we need an adequately powered randomised outcome trial.
Eur J Heart Fail. 2007 Feb;9(2):110-2. Epub 2007 Jan 30 : no abstract

---