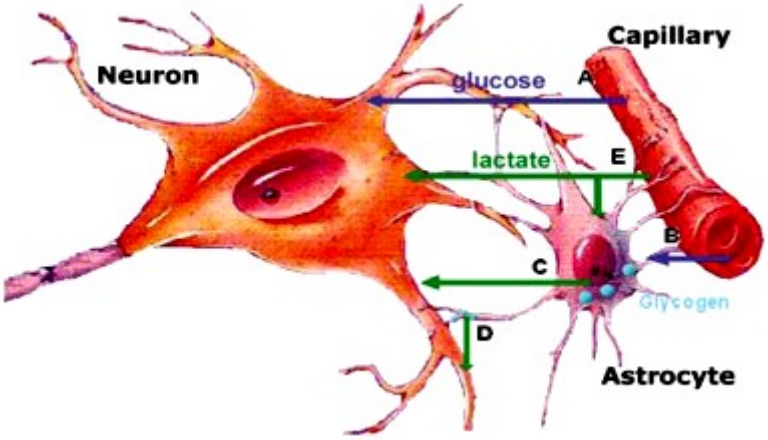
Efficacité de l'érythropoietine

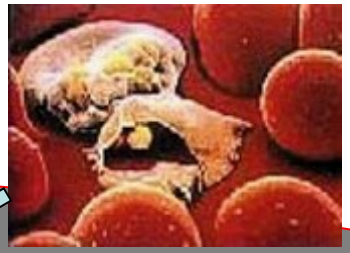
pour le neuropaludisme de l'enfant



Stéphane Picot

Malaria Research Unit, EA 4170
University Claude Bernard Lyon 1
Lyon, France

Apoptosis Highway



Plasmodium falciparum apoptosis.
Picot 1997 TRSTMH

Plasmodium berghei Apoptosis within the mosquito.
Al-Olayan 2002, Int. J. Par.

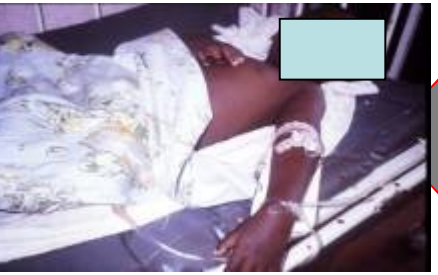
?

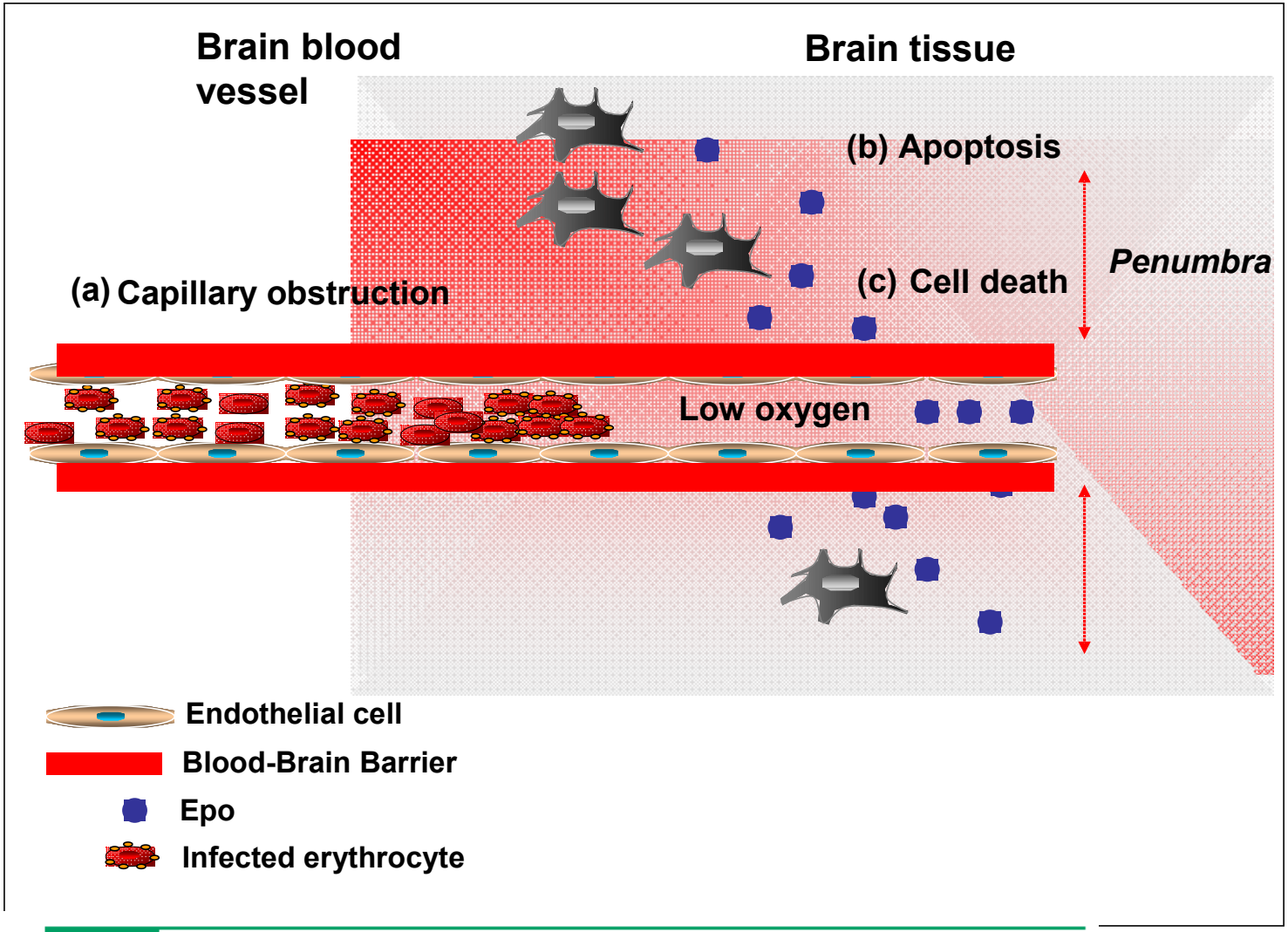
?

EPO control of CM death rate

Kaiser 2006, JID

Endothelial cell death
Pino 2003 JID





Review

Can erythropoietin be used to prevent brain damage in cerebral malaria?

Climent Casals-Pascual[1], Richard Idro[2,3], Stéphane Picot[4], David J. Roberts[5] and Charles R.J.C. Newton[2,6,7]

Essai clinique (clinicaltrial.gov *NCT 00697164)*

- Nouvelle indication
  - 1 : Proof of concept
  - 2 : Randomized double blind clinical trial

- Bamako, Mali
  - Malaria Research and Training Center (O. Doumbo)
  - Gabriel Touré hospital (Severe malaria ward)

- Epoetin beta (NEORECORMON®) 1500 IU/kg/j
- quinine IV 25 mg/kg/day,
- **J 1-3**

- Safety

- Ethical Clearance: Rofar Board of Trustees (CH), FMPOS
- Data monitoring committee:
  - T.Taylor (USA-Malawi), F. Nicolini (France), P. François (France), D. Dialo (Mali)

High-Dose Erythropoietin in Extremely Premature Infants to Prevent/Attenuate Brain Injury: A Phase II Study

This study has been suspended.
(FDA hold)

First Received: December 27, 2007 Last Updated: January 29, 2009 History of Changes

Sponsored by:	**Atlantic Health System**
Information provided by:	Atlantic Health System
ClinicalTrials.gov Identifier:	NCT00589953

Early Communication about an Ongoing Safety Review

Epoetin alfa

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a cause and effect relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

Epo + Quinine

35 patients inclus

28 vivants à J7

80 %

7 décès

20 %

Imputabilité à l'Epo (DMC)

5 patients : Unlikely

mort 1 heure après admission

CQ surdosage avant admission, hypoglycemie, mort H 3

Vomissements incoercibles après nutrition, mort à H 32

diazepam, détresse respiratoire, mort à H 44

Acidose à admission, mort à H 51

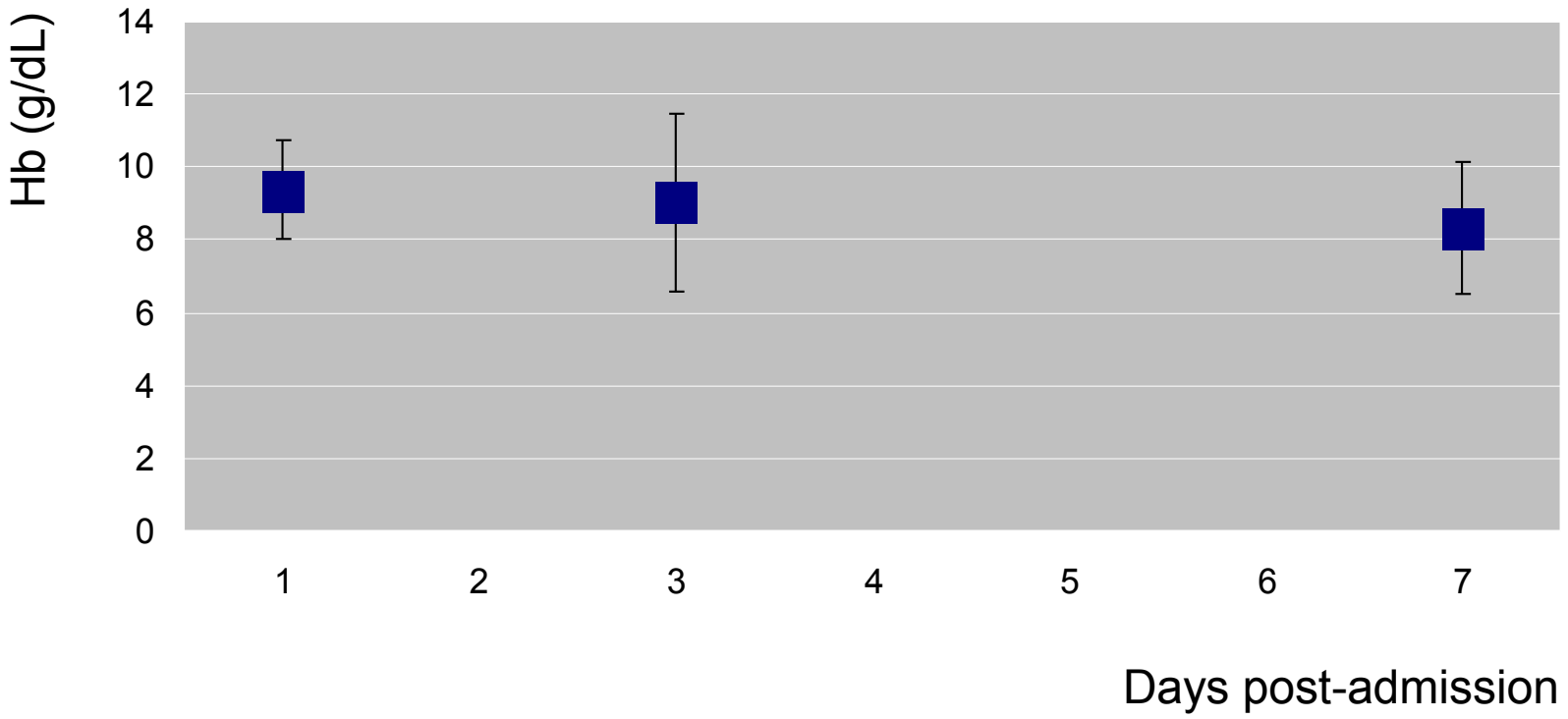
2 patients : Unclassifiable

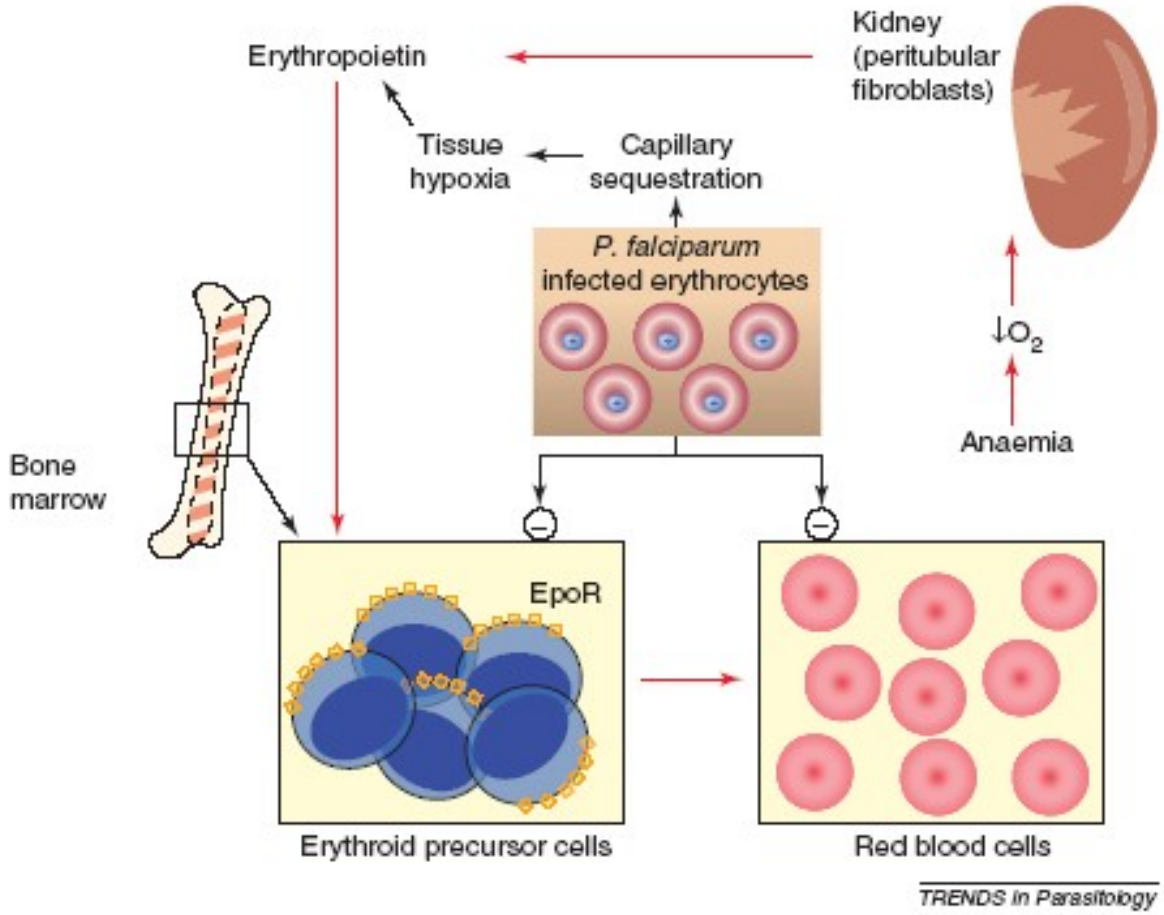
Hypotension, mort H1

Mort H 16

	Intention de traiter	Survivants	Décédés	Comparaison
		n=28	n=7	Vivant/Dcd
Blantyre score = 1	17/35	12/28	5/7	.32
Blantyre score = 2	18/35	16/28	2/7	.16
≥ 1 convulsion(s)	23/35	17/28	6/7	.06
Détresse respiratoire	7/35	4/28	3/7	1
Hémoglobinurie	7/35	6/28	1/7	.55
Ictère	4/35	4/28	0/7	.16

	Intention de traiter	Survivants	Décédés	Comparaison
		n=28	n=7	Vivant/Dcd
SaO2, %	91.0±8.7	89.8± 9.4	95.1±3.5	.10
Asexual *P.falciparum*	43000 ± 62000	45000 ± 46000	37000 ± 54000	.85
Blood pH	7.29±0.1	7.3±0.1	7.3±0.2	.72
Lactates, mmol/L	6.0±3.6	5.8±3.3	6.3±3.6	.78
Hb, g/dL	9.4±1.4	9.6±1.4	9.0±1.2	.32
Glycémie, mmol/L	6.4±3.6	6.3±2.3	7.8±6.1	.54


Hb (g/dL)
14
12
10
8
6
4
2
0
1
2
3
4
5
6
7
Days post-admission



Malaria :

Production inadéquate d'EPO ou suppression érythropoïèse malgré production adéquate ?
(Chang et al, JID 2004)

EPO et malaria non sévère :

Réticulocytose précoce ➪↗replication parasite
Réticulocytose tardive ➪ amélioration récupération

Epo et paludisme sévère

Host	Study type	Cases	Controls	Outcome measure	Refs
Mice	Pre-clinical trial	15 mice given rHu-Epo 50 μg per kg (~120 U per mouse per day) on day 4, 5 and 6 after infection.	15 control mice given saline on day 4, 5 and 6 after infection.	Mortality on day 7 and 8. 6 of 15 on Epo died versus 14 out of 15 on saline.	[48]
Mice	Pre-clinical trial	Mice given rHu-Epo in doses ranging from 1–200 U per day per mouse on different schemes.	Control mice given saline.	Survival on day 14. Survival in controls 0%. Highest survival achieved in mice given 200, 100 or 50 U (i.e. 56%, 48% and 45% of mice survived, respectively).	[51]
Mice	Pre-clinical trial	15 mice were each given pre-mortem low doses of 20 U per day of rHu-Epo, 100 U per day of rHu-Epo, 40 mg per kg per day of artesunate alone or 40 mg per kg per day of artesunate with 20 U per day of rHu-Epo on day 6, 7 and 8 after infection.	15 control mice given saline on day 6, 7 and 8 after infection.	Mortality. All 15 control mice died on day 8. Pre-mortem rHu-Epo of 20 U per day and 100 U per day did not improve survival. Mortality was lower in 40 mg per kg per day of artesunate plus 20 U per day of rHu-Epo with 3 of 15 (20%) mice dying as compared to 40 mg per kg per day of artesunate alone, whereby 6 of 15 (38%) mice died.	[52]
Children	Retrospective study	Children who died (16) or had gross sequelae on discharge (32). Median plasma Epo concentrations were 123 (ranging from 29–1726) U per L and 184 (ranging from 23–694) U per L, respectively.	76 children who survived without sequelae. Median plasma Epo was 278 (with a range of 96–1852) U per L.	Plasma Epo >200 U per L. In a matched analysis, plasma Epo >200 U per L was associated with ~80% reduction in risk of sequelae.	[54]

48 Kaiser, K. *et al.* (2006) Recombinant human erythropoietin prevents the death of mice during cerebral malaria. *J. Infect. Dis.* 193, 987–995

51 Wiese, L. *et al.* (2008) Recombinant human erythropoietin increases survival and reduces neuronal apoptosis in a murine model of cerebral malaria. *Malar. J.* 7, 3

52 Bienvenu, A.L. *et al.* (2008) Artesunate-erythropoietin combination for murine cerebral malaria treatment. *Acta Trop.* 106, 104–108

54 Casals-Pascual, C. *et al.* (2008) High levels of erythropoietin are associated with protection against neurological sequelae in African children with cerebral malaria. *Proc. Natl. Acad. Sci. U. S. A.* 105, 2634–2639

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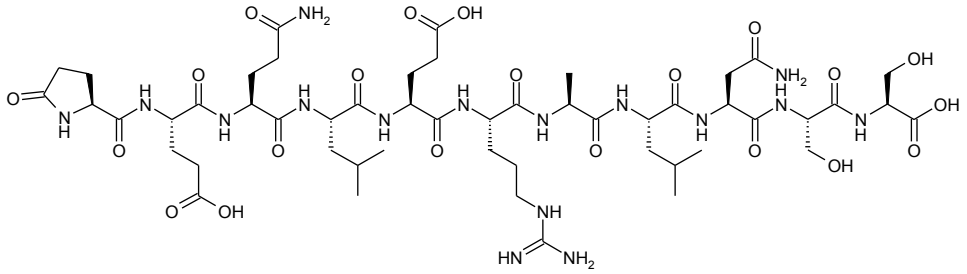
Epopeptides



- 11 amino acid peptides
- Receptor-selective peptides
- Phase I completed

Malaria Research Unit, Lyon

Anne-Lise Bienvenu

RoFAR : Roche Fondation for Anemia Research

Région Rhône-Alpes

Malaria Research & Training Center, Bamako

Ogobara Doumbo

Abdoulaye Djimde

Salimata Konate

Sibiri Sissoko

Abdoulaye Barry

Elisabeth Diarra

Karidiatou Bamba

GlaxoSmithKline

PH Sanchez

Data Monitoring Committee

Terrie Taylor

Franck Nicolini

Patrice François

Dapa Dialo