Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy
www.rbhh.org

Special article

Guidelines on the treatment of anemia of chronic renal failure using recombinant human erythropoietin: Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Guidelines Project: Associação Médica Brasileira – 2014

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ARTICLE INFO

Article history:
Received 11 August 2014
Accepted 2 September 2014
Available online 1 October 2014

Introduction

The guidelines project is a joint initiative of the *Associação Médica Brasileira* and the *Conselho Federal de Medicina*. It aims to collect information to standardize decisions and help create strategies during diagnosis and treatment. These data were prepared and are recommended by the *Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular* (ABHH). Even so, all possible decisions should be evaluated by the physician responsible for diagnosis and treatment according to the patient's setting and clinical status.

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http://dx.doi.org/10.1016/j.bjhh.2014.09.009

Table 1 – Checklist used for critical analysis of the evidence.

Study details	**Sample calculation**
References, study design, Jadad score, strength of evidence	Estimated differences, power, level of significance, total patients
Patient selection	**Patients**
Inclusion and exclusion criteria	Recruited, randomized, prognostic differences
Randomization	**Patient follow up**
Description and blinded allocation	Time, lost to study
Treatment plan	**Analysis**
Intervention, control and blinding	Treatment intervention, analyzed and control
Outcomes considered	**Result**
Primary, secondary, instrument to measure the outcome of interest	Benefit or harm in absolute data. Mean benefit or harm

Description of the evidence collection method

The members of the ABHH Committee responsible for writing the guidelines on the treatment of anemia of chronic renal failure using recombinant human erythropoietin prepared the main question related to its treatment. The issue was structured using the Patient/Problem, Intervention, Comparison and Outcome (PICO) system. The search strategy (Appendix 1) was applied to the primary scientific databases (MEDLINE PubMed, Embase, SciELO and, Lilacs) and secondary scientific database (Cochrane Library).

Methodological quality was assessed using the Jadad score,[1] but this was not used as an exclusion criterion. The critical assessment of the studies considered items with Jadad scores < 3 as inconsistent, and those with scores ≥ 3 consistent. The strength of evidence was analyzed according to the Oxford classification.[2]

Recommendation degree and evidence level (Oxford classification)

A: Experimental or observational studies of better consistency
B: Experimental or observational studies with less consistency
C: Case reports (uncontrolled studies)
D: Opinion without critical evaluation based on consensus, physiological studies or animal models

Background

Usually identified when the glomerular filtration rate falls below 30 mL/min, normocytic normochromic anemia is present in most patients with chronic kidney disease. Although this type of anemia has many causes, it is mainly related to reduced production of erythropoietin, a glycoprotein hormone of 165 amino acids with a molecular weight of 30.4 kDa, responsible for the regulation of erythropoiesis and subsequent maintenance of oxygen homeostasis.[3]

Erythropoietin is a hematopoietic growth factor primarily produced in the kidney cortex, which stimulates the proliferation and differentiation of erythroid progenitor cells in the bone marrow; when erythropoietin is absent these progenitor cells are not protected against apoptosis. Patients with chronic kidney disease gradually develop an inability to produce adequate amounts of erythropoietin to maintain normal hemoglobin levels.[4]

Recombinant human erythropoietin (epoetin alfa and epoetin beta) was produced to meet the needs of these patients by culturing transformed cells from Chinese hamster ovaries and the kidneys of young hamsters. With a half-life of 24 h, epoetin carries complementary DNA that encodes human erythropoietin.[4]

The short half-life of epoetin with the necessity of frequent doses, led the pharmaceutical industry to investigate strategies to prolong the action of the molecule. This resulted in the development of darbepoetin alfa with a half-life of 72 h, and continuous erythropoietin receptor activator (CERA) with a half-life of around 130 h.[4]

Aims

To evaluate the benefits and adverse effects of recombinant human erythropoietin and CERA to treat anemia in dialysis and predialysis kidney disease patients.

Search question

What are the main benefits and adverse effects of recombinant erythropoietin, darbepoetin alfa and CERA used to treat anemia in dialysis and predialysis kidney disease patients?

Studies selection inclusion criteria

All full text clinical randomized controlled trials produced between 1981 and 2014 in Portuguese, English and Spanish were considered for the creation of these guidelines.

The type II error was not used in the selection of studies so as not to impose an even greater limitation on the selection.

According to the PICO system, all patients with chronic renal failure and anemia in dialysis or pre-dialysis were included without age restriction. Interventions included treatment with erythropoietin, CERA or darbepoetin alfa. Conventional treatment and placebo were compared and outcomes were defined with an assessment of therapeutic response, such as the level of hemoglobin and the need for transfusion.

A total of 411 studies were chosen for analysis (PubMed-Medline: 396; Embase: 13 and Scielo/Lilacs and Cochrane via the Biblioteca Virtual en Salud: 2). A total of 352 articles were selected after the first analysis, all were from the primary electronic databases with no other articles being found in a manual search.

Evidence selected in the critical evaluation

The papers were critically evaluated in respect to the inclusion and exclusion criteria and 342 papers were excluded

leaving ten articles to comprise the guidelines. No article was excluded due to the unavailability of the full text. Table 1 was used in the critical analysis of the articles.

Erythropoietin

Stage 5 renal failure patients in chronic peritoneal dialysis with anemia (hematocrit <30%) who received erythropoietin (4000 U three times weekly if hematocrit was <32%, and two times weekly if hematocrit was between 32% and 38%) have improvements in anemia after six to 12 weeks of treatment (number needed to treat [NNT] = 2) when compared to a placebo. There is no increase in the incidence or the severity of adverse events related to the drug. Patients in treatment may have a worsening of blood pressure control (number needed to harm [NNH] = 3)[5] (A).

Anemic patients with pre-dialysis chronic renal failure receiving erythropoietin (50–150 U/kg three times a week) have a better therapeutic response (6% increase in hematocrit from baseline) compared to placebo (NNT = 2). There is no increase in the incidence of adverse events such as high blood pressure, headache, joint pain, swelling, and discontinuation of treatment[6] (A).

Anemic patients (hemoglobin <9 g/dL) on hemodialysis receiving erythropoietin have reduced need for transfusion (NNT = 2), and an elevated risk of increases in diastolic pressure with the need for antihypertensive drugs (NNH = 6)[7–9] (A).

Darbepoetin alfa

In adult patients with chronic renal failure (creatinine >4 mg/dL and creatinine clearance <30 mL/min per 1.73 m^2) and anemia (hematocrit <30%), treatment with darbepoetin alfa at a dose of 0.45 mg/kg subcutaneously, once every two weeks, or treatment with erythropoietin alfa at a dose 90 IU/kg subcutaneously, once per week, compared to treatment without drugs that modify the biological course of disease results in an average 30% increase in the concentration of hemoglobin and improvements in left ventricular ejection fraction, although there is no improvement in renal function[10] (B).

On comparing adult patients on peritoneal dialysis for at least three months with hemoglobin levels between 8 and 12 g/dL under treatment with recombinant erythropoietin to those treated with darbepoetin alfa at a dose of 0.45 mg/kg subcutaneously once every two weeks, the latter group required fewer doses to achieve the same increases in hemoglobin at 24 weeks of follow-up. The most common adverse events are edema and iron deficiency[11] (B).

Treatment of diabetic patients with chronic renal insufficiency (glomerular filtration rate 20–60 mL/min per 1.73 m^2) and anemia (hemoglobin level < 11 g/dL) using darbepoetin alfa, results in significant increases in hemoglobin levels (20% on average) within 24 months. There was a 9.7% reduction in the number of transfusions (NNT = 10), but a 2.4% increase in the occurrence of strokes (NNH = 40). There were no significant differences in mortality or worsening renal function among patients undergoing and not undergoing treatment with darbepoetin alfa. The treatment increases arterial and venous thromboembolic events by 0.9% (NNH = 100) and 1.8% (NNH = 55), respectively. In patients with a history of cancer, there is an increase in disease-related mortality[12] (A).

Moreover, there is a 4% increase in cardiovascular events (NNH = 25) and 2.4% increase in mortality (NNH = 40) in patients with minor responses (increase of less than 2% in hemoglobin levels in the first month of treatment)[13] (A).

Continuous erythropoietin receptor activator (CERA)

In adult patients with chronic renal failure and anemia on hemodialysis or peritoneal dialysis, the use of CERA (dose between 60 and 180 mg for two weeks) compared to treatment with darbepoetin, produces no difference in benefits or adverse events[14] (A).

Closing remarks

Recombinant human erythropoietin has been produced for a long time to improve erythropoiesis, or red blood cell production in patients with chronic renal failure. Synthetic forms with longer half-lives have been developed successfully with resulting improvements in anemia, quality of life and need for transfusion, and time between applications. Hemoglobin levels should be kept between 11 and 12 g/dL to avoid possible increases in cardiovascular events and thromboembolic phenomena[15] (A).

Summary of the evidence

The use of erythropoietin to treat anemia associated to chronic renal failure

Benefit
Treatment with erythropoietin increases hemoglobin levels and reduces the number of transfusions needed.

Adverse effects
Treatment with erythropoietin increases blood pressure, in particular diastolic pressure, and the need of antihypertensive drugs.

The use of darbepoetin alfa to treat anemia associated to chronic renal failure

Benefit
Treatment with darbepoetin alfa increases hemoglobin levels, and reduces the number of doses of medication to obtain the same level of hemoglobin compared to erythropoietin, thereby reducing the number of transfusions. It improves the left ventricular ejection fraction.

Adverse effects
Treatment with darbepoetin alfa increases the incidence of stroke, increases venous and arterial thromboembolic events, increases cancer-related mortality in patients with a history of cancer, and increases mortality and cardiovascular events in patients with poor response.

The use of continuous erythropoietin receptor activator to treat anemia associated to chronic renal failure

In patients with chronic renal insufficiency and anemia, there are no significant differences in benefits or adverse effects comparing the use of continuous erythropoietin receptor activator to treatment with darbepoetin.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bjhh.2014.09.009.

REFERENCES

1. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12. PubMed PMID: 8721797.
2. Associação Médica Brasileira e Conselho Federal de Medicina. Projeto Diretrizes. Níveis de Evidência e Grau de recomendação – Oxford Centre for Evidence Based Medicine. Available from: http://www.projetodiretrizes.org.br/projeto_diretrizes/texto_introdutorio.pdf
3. Powell J, Gurk-Turner C. *Darbepoetin alfa* (Aranesp). Proc (Bayl Univ Med Cent). 2002;153:332–5. Erratum in: Proc (Bayl Univ Med Cent). 2002;15(4):365.
4. Macdougall IC, Ashenden M. Current and upcoming erythropoiesis-stimulating agents, iron products, and other novel anemia medications. Adv Chronic Kidney Dis. 2009;16(2):117–30.
5. Nissenson AR, Korbet S, Faber M, Burkart J, Gentile D, Hamburger R, et al. Multicenter trial of erythropoietin in patients on peritoneal dialysis. J Am Soc Nephrol. 1995;5(7):1517–29. PubMed PMID: 7703390.
6. The US Recombinant Human Erythropoietin Predialysis Study Group. Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anaemia associated with chronic renal failure in predialysis patients. Am J Kidney Dis. 1991;18(1):50–9. Erratum in: Am J Kidney Dis 1991;18(3):420.
7. Laupacis A, Canadian Erythropoietin Study Group. A randomized double-blind study of recombinant human erythropoietin in anaemic hemodialysis patients. Transplant Proc. 1991;23(2):1825–6.
8. Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. Br Med J. 1990;300(6724):573–8.
9. Canadian Erythropoietin Study Group. Effect of recombinant human erythropoietin therapy on blood pressure in hemodialysis patients. Am J Nephrol. 1991;11(1):23–6.
10. Chen HH, Tarng DC, Lee KF, Wu CY, Chen YC. Epoetin alfa and darbepoetin alfa: effects on ventricular hypertrophy in patients with chronic kidney disease. J Nephrol. 2008;21(4):543–9.
11. Li WY, Chu TS, Huang JW, Wu MS, Wu KD. Randomized study of darbepoetin alfa and recombinant human erythropoietin for treatment of renal anemia in chronic renal failure patients receiving peritoneal dialysis. J Formos Med Assoc. 2008;107(11):843–50.
12. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–32.
13. Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363(12):1146–55.
14. Canaud B, Mingardi G, Braun J, Aljama P, Kerr PG, Locatelli F, et al. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. Nephrol Dial Transplant. 2008;23(11):3654–61.
15. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085–98.