Dose Efficiency of Erythropoiesis-Stimulating Agents for the Treatment of Patients With Chemotherapy-Induced Anemia: A Systematic Review

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ABSTRACT

Background: Erythropoiesis-stimulating agents (ESAs) increase red blood cell production in patients with chemotherapy-induced anemia (CIA). In Europe, short-acting ESAs (epoetin alfa, epoetin beta, epoetin zeta, and epoetin theta) and a long-acting ESA (darbepoetin alfa) are available to treat CIA.

Objective: This systematic review aimed to determine potential dose efficiency associated with the use of different ESAs for the treatment of CIA according to European labeling.

Methods: A systematic review of ESA studies with starting doses according to European labeling was conducted according to published methodology. Measures of dose efficiency were defined as mean weekly doses to achieve target hemoglobin level or final dose and dose adjustments (dose increase, decrease, or withheld). Electronic databases and grey literature sources were searched up to July 2012. Data were selected for analysis using an evidence hierarchy and quantitatively analyzed to assess statistical homogeneity. Where pooling of data was not appropriate, a narrative summary with descriptive statistics (medians and ranges) was reported.

Results: Fifty-five studies met the inclusion criteria. Twenty-five studies considered to represent the highest level of evidence were extracted and included in the analysis. The analysis showed a high degree of statistical heterogeneity, often precluding meta-analysis. The patients included in the analysis were representative of those encountered in clinical practice, and patient characteristics were similar between the short-acting and the darbepoetin alfa groups. Mean weekly doses appeared ~30% lower with darbepoetin alfa versus short-acting ESAs (median, 136.5 μg or 27,300 IU [range, 21,560–38,260 IU] vs 38,230 IU [range, 31,634–42,714 IU], respectively), resulting in a mean weekly dose ratio of 1:280. Darbepoetin alfa patients appeared to need fewer dose increases compared with short-acting ESAs (pooled, 0.75%; $I^2 = 21\%$ vs median 26.6% [range, 7.6%–44.6%]) and more dose decreases (median, 74% [range, 57%–75%] vs 22% [range, 2.8%–59%]). A similar percentage of darbepoetin alfa and short-acting ESA patients required a dose to be withheld (20% and 33% [2 studies] vs median 33.2% [range, 12.6%–51.1%]).

Conclusions: Statistical heterogeneity between studies was high, although clinically the studies represented medical practice. Without randomized clinical trials directly comparing darbepoetin alfa and short-acting ESAs, these findings are tentative and future research is warranted. This review shows that good-quality, reliable data from head-to-head trials are lacking. The best available evidence comes from prospective ESA-arm data. Mean weekly doses, dose increases, and dose decreases suggest a dose efficiency for darbepoetin alfa compared with short-acting ESAs. (*Clin Ther.* 2014;36:594–610)

Key words: chemotherapy-induced anemia, darbepoetin, epoetin, erythropoiesis-stimulating agent.

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INTRODUCTION

Anemia is a relatively common condition in people with cancer and can occur due to cancer treatment (chemotherapy-induced anemia; CIA) or the disease itself (anemia of cancer). It has been reported that up to 60% of patients with solid tumors and lymphoma may experience anemia, and that in those patients receiving myelosuppressive chemotherapy and/or radiation, this incidence can rise to 70% to 90%.[1] Platinum-based therapies in particular are well-known to induce anemia due to combined toxic effects on the bone marrow and kidneys.[2]

Options available for the management of CIA include adjustments to the cancer therapy regimen, iron supplementation, and red blood cell transfusions (RBCTs). Erythropoiesis-stimulating agents (ESAs) provide an alternative to RBCTs by increasing RBC production. It has been shown in multiple controlled trials that ESAs can increase hemoglobin (Hb) levels and reduce RBCT requirements.[3] ESAs fall into 2 main categories: (1) short-acting ESAs (epoetin alfa,* epoetin zeta,† epoetin beta,‡, and epoetin theta§); and (2) long-acting ESAs (darbepoetin alfa‖) (**Table I**[4–14]). Short-acting ESAs are generally administered three times per week or once weekly.[4–13] Because darbepoetin alfa has a longer half-life, it can be administered less frequently than short-acting ESAs (every 3 weeks compared with once-weekly dosing),[14] which may lead to payer savings as well as a reduced burden on patients. Research in CIA has suggested that darbepoetin alfa may offer savings with respect to the number of doses required and so has greater dose efficiency to achieve the desired clinical outcome.[15] It has also been shown to be the case in nephrology that, when using an initial conversion ratio of 200:1 between darbepoetin alfa and other ESAs, target Hb values can be maintained and a dose saving can be achieved,[16] but a similar level of evidence has not been reported in cancer patients. The initial conversion ratio (200:1) follows the indication in European labeling for the treatment of CIA to achieve satisfactory Hb targets.[14]

The aim of this systematic review was to use the best evidence available to further investigate relative dose efficiency in CIA patients using the European-recommended initial conversion ratio of 200:1. For the purposes of this review, *dose efficiency* was defined as the mean weekly doses of darbepoetin alfa and short-acting ESAs (including biosimilars) required to achieve target Hb levels in patients with CIA. Additionally, dose adjustments, including increases, decreases, and doses withheld were investigated.

MATERIALS AND METHODS

To reduce the risks for bias and error, this review adhered to a prespecified protocol and methods recommended by the Cochrane Collaboration,[17] and the Centre for Reviews and Dissemination (York, United Kingdom),[18] which are accepted by Health Technology Assessment agencies.

Inclusion/Exclusion Criteria

This review included head-to-head studies comparing darbepoetin alfa with the short-acting ESAs (epoetin alfa, epoetin beta, epoetin theta, and epoetin zeta). We also included ESA-arm data (from retrospective or prospective, single-arm studies or comparative cohort studies/randomized controlled trials [RCTs]) in which only one study arm received a relevant ESA treatment. Dose-finding studies were excluded. Eligible ESA treatments had to be in accordance with current European licensing regulations with respect to the starting dose (**Table I**). Adults aged ≥18 years with any type of nonmyeloid cancer who were receiving chemotherapy or chemotherapy plus radiotherapy in addition to an ESA for the treatment of CIA (but not for anemia of cancer or myelodysplastic syndrome), were included.

Eligible studies were published articles and conference abstracts that reported on the dose efficiency of

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