Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia: comparisons from real-world clinical experience

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Background: The purpose of this paper is to report real-world data on the relative effectiveness of a biosimilar erythropoiesis-stimulating agent (ESA; Binocrit®), and other available ESAs for the treatment of chemotherapy-induced anemia.

Methods: Data were collected retrospectively from single centers in Spain (n=284) and Germany (n=145). Hemoglobin outcomes, transfusion requirements, and serious drug-related adverse events were assessed for each ESA.

Results: Hemoglobin outcomes and transfusion requirements were generally similar in the different ESA treatment groups assessed. No serious drug-related adverse events were recorded in any of the treatment groups.

Conclusion: These data confirm the real-world effectiveness and safety of a biosimilar ESA (Binocrit®) for the treatment of cancer patients with chemotherapy-induced anemia.

Keywords: erythropoiesis-stimulating agents, chemotherapy-induced anemia, biosimilar

Introduction

Patients receiving chemotherapy for cancer frequently experience anemia due to the cytotoxic effect on erythroid precursors in bone marrow. Other chemotherapy agents, particularly platinum-based compounds, can directly affect the cells in the kidney responsible for producing erythropoietin. Patients suffering from chemotherapy-induced anemia (CIA) experience profound effects on their quality of life due to extreme fatigue, reduced physical capacity, and in some cases, impaired cognitive function.

Erythropoiesis-stimulating agents (ESAs) have been shown to steadily increase hemoglobin levels, reduce the need for blood transfusions, and improve overall quality of life. Binocrit® (Sandoz GmbH, Kundl, Austria) is a biosimilar epoetin alfa approved by the European Medicines Agency in 2007 for several indications, including the treatment of CIA. Biosimilar is a regulatory term used to describe medicines with similar properties to that of an approved biological medicine for which the patent has expired. For a biosimilar to be approved by the European Medicines Agency, the manufacturer must demonstrate comparability with the reference product in terms of quality, safety, and efficacy.

Several biosimilar epoetins have been approved by the European Medicines Agency. The uptake of these medicines will depend, in part, on physicians’ confidence in the efficacy and safety of these products. There is currently a lack of data on the relative effectiveness of biosimilar ESAs and other available ESAs (short-acting and long-acting) for the treatment of CIA. Thus, it is important to report real-world clinical
experience data for biosimilars in order for physicians to make informed treatment decisions for their patients. Here we report such data with a biosimilar epoetin alfa (Binocrit®) from two separate centers, one from Spain and one from Germany.

Patients and methods
The findings we report were obtained as part of the normal clinical management of the patients, which was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice. All ESAs were used in accordance with current European labels (ie, patients were receiving concurrent chemotherapy and ESA treatment was initiated at a hemoglobin level ≤10 g/dL).

Spanish center
Data are presented from a retrospective clinical experience audit of CIA treatment with ESAs in a large oncology department, including patients treated by multiple (n=20) physicians. The department is within the 1,300-bed Hospital 12 de Octubre in Madrid, and treated more than 21,000 patients (with more than 56,000 consultations) in 2011. Over the last 3 years, the department has treated more than 500 patients with ESAs.

A total of 274 patients (those who had records/data in relation to their ESA treatment readily available) were included in the present analysis. Patients were treated with biosimilar epoetin alfa 40,000 IU once a week (n=116) or 30,000 IU once a week (n=14), darbepoetin alfa 500 µg every 3 weeks (n=99), or darbepoetin alfa 150 µg once a week (n=45). Use of parenteral iron supplementation was considered for patients with serum ferritin <300 ng/mL and transferrin saturation <20%. The primary aim of ESA treatment was transfusion avoidance, with the requirement for red blood cell transfusion assessed during the period of ESA therapy and for 2 months after the end of therapy. Treatments were also assessed for hemoglobin outcomes at the start and end of therapy. Treatments were combined based on ESA product, rather than product and dose, given the relatively low number of patients who received biosimilar epoetin alfa 30,000 IU once weekly and darbepoetin alfa 150 µg once a week. For hemoglobin, the mean (standard deviation) increase during the study was calculated for each product, and a comparison was performed using a t-test. For transfusion requirements, pooled data for each product (proportion of patients who required a transfusion) was compared using a chi-squared (Pearson) test.

Results
Spanish center
The most common tumor types were non-small-cell lung cancer (30%), breast cancer (12%), head and neck cancer (7%), and ovarian cancer (6%), as shown in Table 1. The most commonly used chemotherapy agents overall were carboplatin

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small-cell lung</td>
<td>84 (29.6)</td>
</tr>
<tr>
<td>Breast</td>
<td>34 (12.0)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>16 (5.6)</td>
</tr>
<tr>
<td>Bladder</td>
<td>14 (4.9)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>13 (4.6)</td>
</tr>
<tr>
<td>Small cell lung</td>
<td>13 (4.6)</td>
</tr>
<tr>
<td>Kidney</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Stomach</td>
<td>9 (3.2)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Prostate</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Cervical</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (9.9)</td>
</tr>
</tbody>
</table>
(108/284 patients) and paclitaxel (68/284 patients); the most common chemotherapy combination was carboplatin/paclitaxel (49/284 patients). Among patients treated with darbepoetin (all doses combined, n=146), the most common regimens were carboplatin/paclitaxel (22 patients), carboplatin/gemcitabine (eight patients), and paclitaxel alone (eight patients). The same three regimens were also the most commonly used in patients who received biosimilar epoetin alfa (all doses combined, n=116): carboplatin/paclitaxel (20 patients), carboplatin/gemcitabine (seven patients), and paclitaxel alone (six patients). Twenty-seven percent of patients received ESA treatment for 4 weeks, and 42% were treated for more than 4 weeks. Mean duration of ESA by treatment group was as follows: biosimilar epoetin alfa 40,000 IU once a week, 4.20 weeks; biosimilar epoetin alfa 30,000 IU once a week, 4.57 weeks; darbepoetin alfa 500 µg every 3 weeks, 4.68 weeks; and darbepoetin alfa 150 µg once a week, 4.98 weeks. The mean overall hemoglobin level prior to treatment was 9.3 g/dL; 19% of patients had a hemoglobin level <8.5 g/dL and 42% had a hemoglobin level <9 g/dL at the start of the study.

The mean overall hemoglobin at the end of the study was 10.8 g/dL. There were no significant differences (P>0.05) between the different treatment groups in terms of hemoglobin level at the start of ESA treatment, hemoglobin levels achieved at the end of the treatment period, or the highest hemoglobin level achieved on ESA treatment (Table 2). The number of patients overall who required a transfusion was low (38 patients, 13.4%), and generally similar across the different treatments. For example, 13 patients (11.1%) in the biosimilar epoetin alfa 40,000 IU once a week group and 11 patients (11.2%) in the darbepoetin alfa 500 µg every 3 weeks group received a transfusion. No serious drug-related adverse events were reported in any ESA group.

### German center

The two cohorts were well matched (Table 3). Most patients in each group had breast cancer (85% of patients in the biosimilar epoetin alfa group and 82% in the darbepoetin alfa group). More than 50% of patients in each group were treated with one of the following chemotherapy regimens: docetaxel/adriamycin/cyclophosphamide or 5-fluorouracil/epirubicin/cyclophosphamide with or without docetaxel. All patients were treated with concomitant intravenous iron along with their ESA therapy.

The mean overall hemoglobin level prior to treatment was 9.85 g/dL and 9.92 g/dL for the biosimilar epoetin alfa and darbepoetin alfa groups, respectively. Hemoglobin outcomes and red blood cell transfusion requirements are shown in Table 4. The mean duration of ESA treatment was 4.66 weeks in the Binocrit® group and 4.28 weeks in the darbepoetin alfa group. The mean hemoglobin level at the end of ESA treatment was 11.91 g/dL in the biosimilar epoetin alfa group and 11.93 g/dL in the darbepoetin alfa group. There were no significant differences (P>0.05) between the two groups in hemoglobin level at the start of ESA treatment or at the end of the treatment. In both treatment groups, the median time to achieve a hemoglobin increase >1 g/dL and 2 g/dL was 2 and 4 weeks, respectively. Four patients (4.2%) in the biosimilar epoetin alfa group and four (8%) in the darbepoetin group required a red blood cell transfusion during the period of ESA treatment. No deaths, thromboembolic events, or other serious adverse drug reactions were observed under ESA treatment.

### Pooled analysis of hemoglobin outcomes and transfusion requirements

Based on pooled data for each product, the mean increase in hemoglobin was 1.98±0.53 g/dL with biosimilar epoetin alfa, and 1.82±0.10 g/dL with darbepoetin alfa (P=0.5). Blood transfusion was required by 18 patients (8%) who received

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### Table 2 Hemoglobin outcomes at the Spanish center

<table>
<thead>
<tr>
<th>ESA</th>
<th>Mean treatment duration (weeks)</th>
<th>Mean Hb at start of treatment (g/dL)</th>
<th>Mean maximum Hb achieved (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darbepoetin 150 µg QW</td>
<td>4.98</td>
<td>9.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Darbepoetin 500 µg Q3W</td>
<td>4.68</td>
<td>9.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Binocrit® 30,000 IU</td>
<td>4.57</td>
<td>9.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Binocrit® 40,000 IU</td>
<td>4.20</td>
<td>9.3</td>
<td>10.7</td>
</tr>
</tbody>
</table>

**Note:** Binocrit® (Sandoz GmbH, Kundl, Austria).

**Abbreviations:** ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; QW, once weekly; Q3W, once every 3 weeks.

### Table 3 Patient characteristics by treatment group at the German center

<table>
<thead>
<tr>
<th>Darbepoetin alfa 500 µg Q3W (n=50)</th>
<th>Binocrit® 40,000 IU QW (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, years</td>
<td>55.6 (11.20)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>41 (82.0)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Cervical</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (6.0)</td>
</tr>
</tbody>
</table>

**Note:** Binocrit® (Sandoz GmbH, Kundl, Austria).

**Abbreviations:** QW, once weekly; Q3W, once every 3 weeks; SD, standard deviation.
cancer and CIA have been revised in recent years to recom-
and avoiding the need for red blood cell transfusions.

darbepoetin once every 3 weeks for raising hemoglobin levels
ment with biosimilar epoetin alfa appears to be as effective as
based on the data from the German center, once weekly treat-
retrospective nature of the study. It is interesting to note that,
clin transfusion requirement favoring biosimilar epoetin alfa.
However, caution is warranted when considering the clini-
in transfusion during esa treatment (weeks)
Mean duration of esa treatment (weeks)
Mean Hb at start of esa treatment (g/dL)
Mean Hb at end of esa treatment (g/dL)
Patients requiring red blood cell transfusion during esa treatment period, n (%)

Table 4 Hemoglobin outcomes and red blood cell transfusion requirements at the German center

<table>
<thead>
<tr>
<th></th>
<th>Darbepoetin alfa 500 μg QW (n=50)</th>
<th>Binocrit® 40,000 IU QW (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of ESA treatment (weeks)</td>
<td>4.28</td>
<td>4.66</td>
</tr>
<tr>
<td>Mean Hb at start of ESA treatment (g/dL)</td>
<td>9.92</td>
<td>9.85</td>
</tr>
<tr>
<td>Mean Hb at end of ESA treatment (g/dL)</td>
<td>11.93</td>
<td>11.91</td>
</tr>
<tr>
<td>Patients requiring red blood cell transfusion during ESA treatment period, n (%)</td>
<td>3 (6.0)</td>
<td>4 (4.2)</td>
</tr>
</tbody>
</table>

Note: Binocrit® (Sandoz GmbH, Kundl, Austria).
Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; QW, once weekly; Q3W, once every 3 weeks.

biosimilar epoetin alfa and 28 patients (14.3%) who received
darbepoetin alfa (P=0.039).

Discussion

Binocrit® is a biosimilar ESA that has been approved for the
treatment of CIA since 2007. Previous studies have demon-
strated the efficacy and safety of this agent for the treatment
of CIA, both in a randomized, controlled trial and also in
real-life clinical practice.12,13 However, to date, there has been
a lack of data on the relative effectiveness of biosimilar ESAs
and other available ESAs in this setting. The availability
of such real-world data is important if physicians are to make
informed treatment decisions when considering options for
ESA treatment. The data presented here confirm the real-
life clinical effectiveness and safety of managing CIA with
biosimilar epoetin alfa. They also indicate that treatment
outcomes are similar when patients with cancer and CIA are
treated with biosimilar epoetin alfa or darbepoetin alfa. The
proportion of patients in both product groups who required
a blood transfusion was low compared with data from previ-
ously published randomized studies.12,14,15 Pooled data from
the two centers showed a statistically significant difference
in transfusion requirement favoring biosimilar epoetin alfa.
However, caution is warranted when considering the clinical
significance of this finding, given the constraints of the retrol-
pective nature of the study. It is interesting to note that,
based on the data from the German center, once weekly treat-
ment with biosimilar epoetin alfa appears to be as effective as
darbepoetin once every 3 weeks for raising hemoglobin levels
and avoiding the need for red blood cell transfusions.

The European labels for the use of ESAs in patients with
cancer and CIA have been revised in recent years to recom-
 mend more conservative use. Current labels advise that
patients must be receiving chemotherapy and that treatment
is initiated at a hemoglobin level ≤10 g/dL, with the aim
of treatment to achieve a hemoglobin level in the range
10–12 g/dL. It is noteworthy that ESA use differed slightly
between the two centers analyzed in this study, while still
falling in line with these recommendations. Hemoglobin
levels at initiation of ESA were higher in the German center
than in the Spanish center, as were the hemoglobin levels
achieved at the end of the ESA treatment period. Despite
these differences in ESA use and practice patterns in the
two centers, no serious drug-related adverse events (includ-
ing thromboembolic events) were reported in either center.

However, these analyses included studies of what would today
be considered off-label use of ESAs (eg, patients not receiv-
ing chemotherapy, initiation of ESA treatment at hemoglobin
levels >12 g/dL).

As mentioned previously, ESA use in our centers reflects
the current, more conservative recommendations and this
may explain why no cases of thromboembolic events were
noted. In the future, adequately designed and appropriately
powered studies would be of interest to determine the impact
of different ESA practice patterns on safety outcomes such
as thromboembolic events.

The potential for ESAs to affect disease progression and/or
mortality in cancer patients has been the subject of much
debate in the literature. Preclinical studies have suggested
that erythropoietin receptor (Epo-R) mRNA and/or protein may be
present in a range of human tumors and cancer cell lines, and
that ESAs have growth-modulating effects on tumor cells.18–20
However, several methodological issues have been raised that
may limit the validity of some of these findings.18,21 These
include use of bulk tumor tissue (which may contain stromal
cells and other cell types that infiltrate from blood) in studies
examining Epo-R mRNA levels, use of commercially avail-
able antibodies for Western blot and immunohistochemistry
analyses that were subsequently shown to lack specificity
for Epo-R, and use of supraphysiological ESA doses. More
recently, new antibodies have been developed that appear to
have improved specificity for Epo-R;22 such antibodies may
become valuable new tools in this area of research. A num-
ber of clinical studies have also contributed to concerns that
ESAs may impact disease progression and overall survival
in patients with cancer, although it is important to highlight
that these involved use of ESAs that would now be considered
off-label (eg, target hemoglobin levels in excess of 14 g/dL,

Note:
- Hb, hemoglobin
- ESA, erythropoiesis-stimulating agent
- QW, once weekly
- Q3W, once every 3 weeks
patients who were not receiving chemotherapy).\textsuperscript{23–26} These and other studies have prompted several meta-analyses to assess the use of ESAs and safety outcomes in patients with cancer.\textsuperscript{17,27–30} Importantly, none of these has identified an adverse effect of ESA use on survival when considering studies in patients with CIA. Similarly, based on the balance of evidence to date from clinical trials, ESAs do not have an adverse effect on disease progression.\textsuperscript{21,30}

In many countries, expenditure on health care is increasing to unsustainable levels, with cancer medicines a leading driver of these increases.\textsuperscript{31} Use of biosimilar medicines has been identified as one way of controlling these escalating costs. A recent study evaluated the comparative cost efficiency of different ESAs under different scenarios of fixed and weight-based dosing in the management of CIA.\textsuperscript{32} Managing CIA with biosimilar epoetin alfa was shown to be consistently cost-efficient over treatment with originator epoetin alfa, epoetin beta, and darbepoetin alfa (both once weekly and once every 3 weeks) under both fixed and weight-based dosing scenarios. Patient exposure to biosimilars continues to increase as adoption of these agents becomes more widespread. For example, the current (as of February 2014) estimated exposure to Binocrit\textsuperscript{33} is over 300,000 patient-years, with more than 5,000 patients studied in clinical trials.\textsuperscript{33} A recent review identified no difference in safety profiles between biosimilar and reference products.\textsuperscript{34} Similarly, a prospective randomized clinical study, conducted since licensing, demonstrated equivalent pharmacokinetic and pharmacodynamic profiles, safety, and clinical efficacy between originator and biosimilar epoetins.\textsuperscript{35}

As indicated previously, a clear limitation of our data is that they were generated from retrospective chart reviews rather than in a randomized, controlled setting; an adequately designed, prospective study is necessary to confirm our findings. Nevertheless, reporting of such real-world data is of use to physicians when considering the choice of ESA therapy for patients with cancer and CIA.

In summary, data from these single-center audits confirm the real-world effectiveness and safety of biosimilar epoetin alfa (Binocrit\textsuperscript{5}) for the treatment of cancer patients with CIA. The findings should inform and reassure physicians when making treatment decisions on use of ESAs in this setting.

Disclosure

FRL and MT are employees of Sandoz. The other authors have no conflicts to declare. Medical writing assistance in the preparation of this paper was provided by Tony Reardon of Spirit Medical Communications Ltd and funded by Sandoz International GmbH.

References


