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Biosimilar epoetin α is as effective as originator epoetin-α plus liposomal iron (Sideral®), vitamin B12 and folates in patients with refractory anemia: A retrospective real-life approach

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Abstract. Several biosimilar versions of recombinant human erythropoietin are currently approved for use in Europe, including a biosimilar epoetin-α. The aim of this the study was to verify that biosimilar epoetin-α is similar in terms of efficacy, safety and cost to originator epoetin-α for the treatment of refractory anemia in patients with myelodysplastic syndrome. A total of 92 patients with myelodysplasia and refractory anemia were investigated. The patients received either originator (group A) or biosimilar (group B) epoetin-α. In addition, they received liposomal iron (Sideral®), calcium levofolinate and vitamin B12. Moreover, the median monthly overall costs were calculated for each group. The results demonstrated that hemoglobin (Hb) levels increased by 1 g/dl after a median time of 5 weeks in group A and 4 weeks in group B. In group A, a Hb level of >12 g/dl was achieved after 12 weeks, while in group B after 10.5 weeks. The median cost of therapy was 1,536 euros/month in group A and 1,354 euros/month in group B. A total of 5 patients required transfusion support in group A and 7 in group B. In conclusion, biosimilar epoetin-α appears to be comparable to originator epoetin-α in terms of efficacy and safety for the treatment of refractory anemia.

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Introduction

Biosimilar drugs are similar, but not identical, versions of biological medicines that have already been approved. 'Biosimilar' is a regulatory term used to indicate a biopharmaceutical product that has been approved under a well-defined regulatory pathway, such as the one established by the European Medicines Agency (EMA). Several biosimilar versions of recombinant human erythropoietin are currently approved for use in Europe, including a biosimilar epoetin-α (HX757). HX575 is a biosimilar version of human recombinant erythropoietin (epoetin-α) that was approved for use in Europe in 2007 under the EMA biosimilar approval pathway. HX575 was approved by the EMA in Europe after it exhibited similarity/comparability to originator epoetin-α in terms of protein structure, equivalence with respect to pharmacokinetic and pharmacodynamic profiles and comparable clinical efficacy and safety profiles in studies (1-3). Although the use of erythropoiesis-stimulating agents (ESAs) for low-risk patients with myelodysplastic syndromes (MDS) is currently supported by all major MDS treatment guidelines regarding hematopoietic growth factors (4-8), data on the use of biosimilar ESAs in this population are lacking. The aim of this study was to determine whether HX575 is similar in terms of efficacy, safety and cost to originator epoetin-α for the treatment of refractory anemia in patients with MDS.

Materials and methods

Patients. Between July, 2008 and June, 2012, a total of 92 MDS patients with refractory anemia were included in the study. The patients included 45 men and 47 women, with a median age of 75 years (range, 60-81 years). Patients with the 5q- syndrome were excluded from the study. A total of 29 patients exhibited chromosomal abnormalities, namely loss of the Y chromosome (n=3), 20q- karyotype (n=2), trisomy of chromosome 8 (n=2) and other chromosomal abnormalities (n=22), excluding loss of chromosome 7, 5q- and complex karyotype. The main comorbidities were type 2 diabetes in 32 patients, chronic obstructive pulmonary disease (COPD) in 22 patients, congestive heart failure (CHF) in 11 patients and other chronic diseases in 18 patients. All the patients had anemia following a complete blood count and had an International Prognostic Scoring System value low or intermediate-1.

All the procedures followed were in accordance with the ethical standards of the responsible Committee on Human Experimentation and with the principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Laboratory evaluation. This was a two-centre, non-randomized, retrospective study. All the patients underwent complete blood count, bone marrow aspiration, renal and liver function tests and bone marrow karyotyping at diagnosis. We also measured the endogenous erythropoietin level, vitamin B12 level, folate, ferritin, transferrin, transferrin saturation, blood iron content and erythrocyte sedimentation rate. The patients received epoetin-α if the hemoglobin (Hb) level was <10 g/dl, as suggested by Italian Society of Hematology guidelines (9).

Treatment. Patients with Hb levels <12 g/dl received supportive treatment with epoetin-α if symptomatic. All the patients received supportive treatment with vitamin B12 (400 mg/day orally) and calcium levofolinate (7.5 mg/day orally), in order to support erythropoiesis and prevent vitamin B12 and folate deficiency subsequent to erythropoiesis stimulation. Patients with normal or high ferritin levels and transferrin saturation 10-20% received 2 capsules of oral liposomal iron daily (Sideral®; PharmaNutra, Pisa, Tuscany, Italy) during erythropoiesis support (each capsule containing 14 mg iron + ascorbic acid 60 mg + vitamin B12). Patients with low ferritin or transferrin saturation <10% were excluded from the study. The patients received either originator (group A, n=46) or biosimilar (group B, n=46) epoetin-α 40,000 IU weekly by subcutaneous administration. When a Hb level of 12 g/dl was achieved, the patients received a maintenance dose of 40,000 IU epoetin every 2 weeks. If Hb level subsequently decreased, weekly administration was resumed; if Hb level increased, epoetin was administered at intervals of once every 3 weeks or more.

Follow-up. All the patients underwent monthly physical examination, complete blood count and blood renal and liver function tests; they also underwent monthly measurements of vitamin B12 level, folate, ferritin, transferrin, transferrin saturation and blood iron content. A patient was considered to be a non-responder if the Hb level did not increase ≥1.5 g/dl after 3 months of epoetin treatment (9). The data reported herein are from the cohort of patients who responded to epoetin in each group. The monthly treatment cost per patient was calculated by dividing overall costs (including drug costs, transfusion costs, cost of disposable items and nursing/medical work cost) by the number of months of observation; the median monthly overall cost for each group was then determined.

Table I. Patient characteristics at the initiation of the study (n=92).

Characteristics	Group A	Group B
Gender		
Male/female	18/28	25/21
Age, years		
Median (range)	70 (63-75)	66 (60-81)
Karyotype		
Low-risk	30	32
Intermediate	13	11
Not evaluable	3	3
Comorbidities		
NIDDM	18	14
COPD	14	8
CHF	5	6
Hb level, g/dl		
Median (range)	8.5 (8-11)	9.2 (8.5-11.5)
Basal epoetin level		
Availability	15/46 (32%)	21/46 (46%)
Inappropriate	5/15 (33%)	9/21 (43%)

NIDDM, non-insulin-dependent diabetes mellitus; COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure; Hb, hemoglobin.

Results

Patient characteristics. The characteristics of the patients in each group are listed in Table I. The median Hb at the initiation of treatment was ~8.5 g/dl in group A and 9.2 g/dl in group B. Data regarding basal erythropoietin levels were available for only 15 patients in group A (32%) and 21 patients in group B (46%). Inappropriate levels of basal erythropoietin were observed in 5 patients in group A and in 9 patients in group B.

Follow-up. The results are summarized in Table II. The median follow-up was 22 months (range, 3-34 months). A total of 2 patients in group A with COPD and a Hb level of 11 g/dl and 2 patients in group B with CHF and Hb levels of 11 and 11.5 g/dl, received transfusions for symptomatic anemia. In group A, 2 patients succumbed to disease progression and 1 patient to myocardial infarction. In group B, 2 patients succumbed to disease progression, 1 to sepsis in a background of non-insulin-dependent diabetes mellitus and 1 due to hemorrhage. In group A, 1 patient reported headache and

2 reported an increase in blood pressure. In group B, 2 patients reported headache and 2 an increase in blood pressure. In group A, 23 patients (50%) responded to originator epoetin and in group B, 20 patients (43%) responded to biosimilar epoetin treatment. Transfusion support was required for 5 patients in group A and 7 in group B.

Treatment effectiveness. The Hb level increased by 1 g/dl after a median time of 5 weeks (range, 4-9 weeks) in group A and 4 weeks (range, 3-8 weeks) in group B. In group A, a Hb level of >12 g/dl, with a consequent epoetin dose reduction, was achieved after a median of 12 weeks (range, 4-18 weeks); in group B, a Hb level of >12 g/dl, with a consequent epoetin dose reduction, was achieved after a median of 10.5 weeks (range, 3-16 weeks). A maintenance dose was administered with a median of every 2 weeks (range, 2-4 weeks) in group A, while in group B a maintenance dose was administered with a median of every 3 weeks (range, 2-5 weeks). A total of 5 patients in group A and 7 patients in group B required transfusion support. Loss of response to epoetin was observed in 2 patients in group A and 3 patients in group B.

Table II. Summary of main results.

Results	Group A	Group B
Symptomatic patients transfused, no. (Hb, g/dl)		
COPD	2 (11)	-
CHF	-	2 (11 and 11.5)
Patients responding to EPO treatment, no. (%)	23 (50)	20 (43)
Patients deceased, no.		
PD	2	2
MI	1	-
Sepsis in NIDDM	-	1
Hemorrhage	-	1
Side effects, no.		
Headache	1	2
Increased blood pressure	2	2
Patients transfused, no.	5	7
Median time for increase of Hb level by 1 g/dl with EPO, weeks (range)	5 (4-9)	4 (3-8)
Time-to-reduction of EPO after achieving Hb 12 g/dl, weeks (range)	12 (4-18)	10.5 (3-16)
Interval of maintenance dose, weeks (range)	2 (2-4)	3 (2-5)
Median cost of EPO therapy, euros/month (range)	1,536 (1,240-1,850)	1,354 (954-1,550)
Patients exhibiting loss of response to EPO, no.	2	3

EPO, epoetin; NIDDM, non-insulin-dependent diabetes mellitus; COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure; PD, progressive disease to overt acute myeloid leukemia; MI, myocardial infarction; Hb, hemoglobin.

Discussion

It has been demonstrated that Hb levels may be increased with epoetin-α treatment in patients with MDS and other conditions characterized by bone marrow failure (10-14). However, data regarding the use of HX757 in MDS are currently lacking.

ESA monotherapy typically results in erythropoietic response rates of 20-30% in the general MDS population. Response rates are higher when patients are carefully selected based on pretreatment serum erythropoietin level or other factors. The median duration of ESA response is ~2 years and is, on average, longer among patients who achieve a larger treatment-associated Hb increment compared with those who experience only a minor Hb increase (15,16).

In 1995, Hellström-Lindberg (17) reviewed 205 patients with MDS treated with ESAs in 17 small studies and identified three major factors as predictive of a Hb response, namely pretreatment serum erythropoietin level <200 U/l, a form of MDS other than refractory anemia with ringed sideroblasts and absence of a red blood cell transfusion requirement. A total of 4 patients in groups A and B (2 per group) succumbed due to disease progression to leukemia. Based on currently available evidence, progression to leukemia is unlikely to be the result of epoetin treatment. A prospective clinical trial of ESAs in MDS (ECOG E1996 trial) evaluated the efficacy and long-term safety of epoetin, with or without granulocyte colony-stimulating factor plus supportive care (SC; n=53) vs. SC alone (n=57) for the treatment of anemic patients with lower-risk MDS (18). The presence of older patients with more comorbidities and the lack of data regarding basal serum epoetin level may explain the marginally worse time-to-response to epoetin and the most frequent administration of maintenance epoetin dose in group A. In fact, older age was identified as an adverse prognostic factor in a number of different MDS prognostic scoring systems (19-21). A subsequent study demonstrated that only a limited number of patients with pretreatment serum erythropoietin levels >500 U/l respond to ESA therapy (22).

The proportion of patients in our study responding to epoetin was similar between the originator and biosimilar epoetin-α groups. Overall, 43 of the 92 patients (47%) exhibited a response to epoetin; this proportion was higher compared with that reported in the literature (23), although the lack of data regarding endogenous erythropoietin level for some patients and the low number of patients included make it difficult to draw meaningful conclusions based on response rate.

With prolonged follow-up (median, 5.8 years), no differences were observed in the overall survival of patients in the epoetin vs. SC arms (median, 3.1 vs. 2.6 years, respectively) or in the incidence of transformation to acute myeloid leukemia (7.5 and 10.5% of the patients, respectively). Other adverse effects, such as headache and small increases in

blood pressure, occurred with a similar incidence in the two treatment groups and are not considered clinically relevant.

The cost analysis in our study suggested lower overall costs in the group who received biosimilar epoetin-α compared with that in the group that received originator epoetin-α, although these findings require confirmation using more robust measures of cost-effectiveness, such as quality-adjusted life years.

The rationale behind the use of liposomal iron is that patients with MDS frequently exhibit a functional deficit of iron, with elevated ferritin levels and low transferrin saturation (<20%). In these patients, an increase in the level of the protein hepcidin is observed, which inhibits intestinal iron absorption and iron release from tissue macrophages (24). In patients with functional iron deficiency, intravenous (i.v.) iron may be effective in supporting erythropoiesis, although several studies have demonstrated oral iron to be ineffective (25-28). However, the results of preliminary studies indicate that oral liposomal iron may be as effective as i.v. iron in myelodysplastic and neoplastic patients (29-31). For this reason, the patients in our study received oral liposomal instead of i.v. iron. Our study had several limitations, including its retrospective nature, the absence of data regarding basal serum endogenous erythropoietin for all the patients and the limited number of patients (responders) evaluated (43/92). However, despite these limitations, biosimilar epoetin-α appears to be as safe and effective and potentially more cost-effective compared with originator epoetin-α for the treatment of MDS patients with refractory anemia.

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