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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Comparative risk/benefit profile of biosimilar and originator erythropoiesis-stimulating agents (ESAs): data from an Italian observational study in nephrology

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Abstract

Purpose The aim of this multicenter prospective study was to evaluate efficacy and safety of biosimilar erythropoiesis-stimulating agents (ESAs) vs originator, based on data from clinical practice in patients with chronic kidney disease (CKD).

Methods We collected data of the patients with diagnosis of CKD on conservative treatment from nine Italian structures. Patients were enrolled applying different exclusion criteria, and various individual parameters were registered at the beginning for descriptive analysis. Patients were treated with epoetin alfa, beta, and darbepoetin as originator and epoetin zeta as biosimilar. Hemoglobin levels have been analyzed at baseline and after 3, 6, and 12 months. Descriptive statistics were used to analyze the results.

Results At baseline, 47 patients were in the biosimilar group and 57 in the originator; the basal level of hemoglobin was similar between the groups (mean Hb 9.4 and 9.3 g/dL, respectively). Median age, weight, and comorbidities were almost comparable. After 3 months, 44 patients remained in the biosimilar group and 48 in the originator; hemoglobin increase was significantly greater in patients treated with biosimilar [absolute increase 1.6 vs 1.0 g/dL, $p < 0.001$]. After 6 and 12 months, number of patients fall furthermore. Hemoglobin levels increased more in the biosimilar group after 6 months (2.1 vs 1.1 g/dL, $p < 0.001$) and 12 months (2.0 vs 1.0 g/dL, $p < 0.001$).

Conclusions Biosimilar ESAs have similar risk/benefit profile compared to originators. Our data are in agreement with relevant scientific literature and, on the other hand, they are in contrast with common thought that considers biosimilar less efficacious and less safe than originators.

Keywords Biosimilar · Erythropoiesis-stimulating agents · Risk/benefit profile · Observational study

Introduction

Erythropoiesis-stimulating agents (ESAs) include the recombinant erythropoietin and its synthetic derivatives such as epoetin alfa, epoetin beta, darbepoetin alfa, and others. They are widely used especially for the treatment of anemia due to chronic kidney disease (CKD) or myelosuppressive chemotherapy [1]. The introduction of recombinant ESAs in 1989 resulted in a major progress in the treatment of anemia related to CKD. Patent expiration of epoetin alfa in 2004 started the marketing of the corresponding biosimilars that are active substances similar (but not identical) in efficacy and safety to the reference branded product and represent a therapeutic option cheaper than originator. All the biological drugs contain active ingredients obtained from biological sources, and they differ from chemically synthesized products because of

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their structure and the articulate production process. In Europe, the risk/benefit profile of biosimilars vs originators is investigated through a stepwise head-to-head comparison [2] to demonstrate the absence of clinically meaningful differences in terms of quality, safety, and efficacy of a biological product against the reference product [3]. Apart from the regulatory process of biosimilars, which may raise some doubts as in the case of efficacy and safety data extrapolated from other therapeutic indications, these drugs have been in clinical use for over a decade and the lack of occurrence of noteworthy safety problems should reassure about the clinical overlap of these drugs compared to the originator. However, in some therapeutic areas, such as nephrology, biosimilars still produced skepticism by clinicians and patients, in particular about their real effectiveness and safety compared to the originators. We aimed to compare the patterns of drug use of originator and biosimilar erythropoietins and their safety profiles in patients with chronic kidney disease in the real clinical practice in Italy.

Methods

Data source and study population

This study was a prospective, national, multicenter, drug-utilization observational study. It was performed with the collaboration of the nephrology and pharmacy units of the participating centers. The CINECA Interuniversity Consortium provided a secure web-based data collection system and support for descriptive statistical analysis, and the department of Medical and Surgical Sciences (unit of Pharmacology) provided scientific coordination.

The primary aim was to compare the weekly prescribed doses (UIs) by type of erythropoietin (biosimilar vs originator) in relation to variations in hemoglobin levels, with the possibility to determine whether the real prescribed daily dose (PDD) of biosimilar and originators are superimposable or significantly different. The secondary aim was to compare the safety profile of these drugs by detection of suspected adverse drug reactions (ADRs).

The study was performed from September 2014 to July 2016. Participating centers were (1) Azienda Ospedaliero-Universitaria of Ferrara, (2) Azienda Ospedaliera ULSS 19 of Andria, (3) Ente Ecclesiastico Ospedale generale Regionale "F.Miulli" of Acquaviva delle Fonti, (4) Farmacia P.O Abele Ajello of Mazara del Vallo, (5) A.O. Fatebenefratelli e Oftalmico of Milano, (6) Nefrologia e dialisi, AO *G. salvini* Garbagnate, (7) Azienda USL Valle d'Aosta, (8) ASUR Marche AV3 Macerata, and (9) AO Ospedali Riuniti Marche Nord (Coordinating Centre).

The study was approved by the Ethic Committee of the Coordinating Centre and was notified to the Ethic Committees of the other participating centers. Patients were enrolled applying the following inclusion criteria: chronic kidney disease in conservative therapy, age > 18 years, first prescription of subcutaneous erythropoietin according to the Summary of Product Characteristics (SPC) of the corresponding medicinal products. Exclusion criteria were patients on dialysis already receiving ESAs or patients who received off-label prescription of ESAs. All enrolled patients signed the informed consent.

For each enrolled patient, the following general and health data were collected during the first visit and after 3, 6, and 12 months follow-up: age, gender, weight, medical examination date, glomerular filtration rate (GFR) using the Cockcroft-Gault formula (ml/min), hemoglobin level (g/dL), type of epoetin used (name, route of administration, dose, and frequency of administration), concomitants drugs, and ADRs.

Statistical analysis

Descriptive statistics methods were used to analyze the results (mean, SD, median, range, and inter-quartile range). They were calculated for all continuous variables, while frequency distributions were reported for categorical variables (gender, disease stage, comorbidities, ADR occurrence). Any imbalances between the two treatment groups were assessed by inferential statistical tests such as the *t* test for continuous variables and the chi-square test for categorical variables.

ANOVA (F test) were also used to test hypotheses on multiple-group comparisons. Unless otherwise stated, all values of *p* values are intended as "two-tailed". In this observational study, propensity score techniques were also applied in order to ensure comparability between the two treatment groups. The log odds of the probability of receiving biosimilar treatment ("logit") were considered as a function of confounding factors (demographic characteristics, baseline clinical characteristics, comorbidities considered clinically significant, and concomitant treatments).

Inverse probability weighting (weighting each patient who was treated with biosimilar by the inverse of the probability that he or she would be selected for biosimilar treatment) was then used to adjust for differences between the two treatment groups obtaining a more accurate treatment effect estimation.

The web-based system for data collection was the CINECA AXMR® (Advanced eXtended Multicentre Research) technology, web-based IT infrastructure specifically designed for clinical research processes management. Data management activities (DB freezing, intermediate tables, views, and materialized views in support of the analysis) were carried out using PL/SQL Developer (database of Oracle Corporation). Data analysis was performed using R open source software (http://www.r-project.org) version 3.2.2.

Results

Up to July 2016, 117 patients from nine participating centers were recruited, 105 (90%) were eligible for study criteria, and 104 started the therapy. Patients' flow chart is available in the supplementary material (Fig. S1). Table 1 shows the demographic characteristics as well as co-comorbidities and concomitant therapies of the sample.

Table 1 Patient baseline characteristics

Parameters	Biosimilar	Originator
Gender		
Male	28 (59.6%)	36 (63.2%)
Female	19 (40.4%)	21 (36.8%)
Total	47	57
	p value = 0.708	
Age		
Mean (SD)	74.9 (11.1)	72.9 (10.8)
Range	[48; 95]	[36; 92]
	p value = 0.358	
Body mass index (BMI)		
Mean (SD)	26.0 (4.5)	27.3 (6.5)
Range	[17.7; 37.8]	[17.6; 60.5]
	p value = 0.256	
Kidney function (GFR stages)		
1. GFR normal		
Number (%)	1 (2.1%)	0 (0%)
2. Mild decrease in GFR		
Number (%)	0 (0%)	7 (12.3%)
3. Moderate decrease in GFR		
Number (%)	19 (40.4%)	26 (45.6%)
4. Severe decrease in GFR		
Number (%)	19 (40.4%)	18 (31.6%)
5. Kidney failure—uricemy		
Number (%)	8 (17.0%)	6 (10.5%)
	p value = 0.074	
Comorbidity		
Cardiovascular disease (%)	63.8%	42.1%
	p value = 0.027	
Hypertension (%)	87.2%	63.2%
	p value = 0.005	
Cancer/hematologic disorders (%)	10.6%	12.3%
	p value = 0.794	
Thyroid disease (%)	17.0%	8.8%
	p value = 0.201	
Diabetes (%)	46.8%	36.8%
	p value = 0.340	
Other disorders* (%)	48.9%	29.8%
	p value = 0.046	
Concomitant therapies		
Low-proteic diet (%)	25.5%	29.8%
Pharmacological therapy (%)	93.6%	89.5%
Antihypertensive (%)	86.4%	82.4%
Phosphorus binders (%)	9.1%	5.9%
Iron supplements (%)	38.6%	39.2%
Folic acid (%)	20.5%	5.9%
Sodium bicarbonate (%)	13.6%	9.8%
Diuretics (%)	68.2%	62.7%
Inotropic agents (%)	15.9%	15.7%
Vitamin D (%)	36.4%	27.5%

*Abnormalities in lipoprotein metabolism, dyslipidemia, diverticular disease, hyperparathyroidism, parathyroid disorders and atherosclerosis, prostate hyperplasia, and other prostate disturbances

The patients came from various geographic areas of Northern, Central, and Southern Italy. Of the 104 patients evaluated at baseline, 57 (55%) received a prescription of originators (33 darbepoetin alfa, 18 epoetin beta, and 6 epoetin alfa) and 47 (45%) a biosimilar erythropoietin (epoetin zeta). Male patients were 63.2% of the originator group (36.8% female) and 59.6% of the biosimilar group (40.4% female); the average age was 72.9 and 74.9 years for originator and biosimilar, respectively. Mean body mass index (BMI) was 26.0 for biosimilar and 27.3 for originator. According to baseline level of kidney function (GFR stages according to the Cockcroft-Gault formula (ml/min) [4]), 26 patients in the originator group and 19 in the biosimilar group had stage 3 chronic kidney disease (45.6 and 40.4%, respectively), 18 patients in the originator group and 19 in the biosimilar group had stage 4 (31.6 and 40.4, respectively), and 6 patients in the originator group and 8 in the biosimilar group had stage 5 (10.5 and 17.0, respectively): no statistical difference was observed between the two groups. Most patients had comorbidities and received several other drugs. The only statistically significant difference between the baseline characteristics of population in the two arms was observed for concomitant hypertension (63.2% in originator group vs 87.2% in biosimilar group, $p = 0.005$). The average weekly prescribed dose was 72.9 UI/Kg (sd = 28.02) for biosimilar, 106.5 UI/Kg (sd = 59.90) for epoetin alfa, 184.0 UI/Kg (sd = 184.12) for epoetin beta, and 95.2 mcg/Kg (sd = 63.8) for darbepoetin alfa ($p < 0.001$). Table 2 shows baseline and follow-up levels of hemoglobin (g/dL). Mean baseline Hb levels were not statistically different between groups—9.3 g/dl for originator vs 9.4 g/dl for biosimilar ($p = 0.652$). At the first follow-up (3 months), data were available for 44 patients in the biosimilar group and 48 in the originator group: mean Hb level was significantly increased in the biosimilar group compared to originator (11.0 vs 10.3 g/dl, $p < 0.001$). Compared to baseline data, the mean absolute increase was 1.6 g/dl for biosimilar and 1.0 g/dl for originator. A similar trend was observed comparing biosimilar data against patients exposed to darbepoetin alfa (11.0 vs 10.6 g/dL respectively, $p = 0.015$). At 6 month follow-up, the analysis was performed on 42 patients in the biosimilar group and 44 in the originator group. Again, mean Hb level was significantly higher in the biosimilar compared to the originator patients (11.5 vs 10.4, $p < 0.001$). Hb level increase form baseline of 2.1 g/dl (mean) in the biosimilar group compared to 1.1 g/dl in the originator group. At 12 month follow-up, data were available only for 19 patients in the biosimilar group (time 0 = 47, 3 months = 44, 6 months = 42) and 16 in the originator group (time 0 = 57, 3 months 48, 6 months = 44). Mean Hb level was 11.4 g/dl in the biosimilar group and

Table 2 Basal and follow-up levels of Hb (g/dL)

Level of Hb (g/dL)	Biosimilar	Originator
Basal		
Number of patients	47	57
Hb (g/dL) mean (SD)	9.4 (0.85)	9.3 (1.23)
Hb (g/dL) range	[7.4; 11.0]	[6.6; 11.6]
	$p = 0.652$	
3 months follow-up		
Number of patients	44	48
Hb (g/dL) mean (SD)	11.0 (1.31)	10.3 (1.35)
Hb (g/dL) range	[8.7; 14.6]	[7.5; 14.6]
Δ vs basal (g/dL) mean (SD)	1.6 (1.28)	1.0 (1.17)
	$p < 0.001$	
6 months follow-up		
Number of patients	42	44
Hb (g/dL) mean (SD)	11.5 (1.36)	10.4 (1.25)
Hb (g/dL) range	[8.6; 15.3]	[7.8; 13.0]
Δ vs basal (g/dL) mean (SD)	2.1 (1.27)	1.1 (1.02)
	$p < 0.001$	
12 months follow-up		
Number of patients	19	16
Hb (g/dL) mean (SD)	11.4 (1.14)	10.3 (1.12)
Hb (g/dL) range	[9.2; 14.0]	[8.0; 12.6]
Δ vs basal (g/dL) mean (SD)	2.0 (1.04)	1.0 (1.07)
	$p < 0.001$	

10.3 g/dl in the originator group ($p < 0.001$). Absolute mean increase from baseline was 2.0 g/dl for biosimilar and 1.0 g/dl for originators.

As far as the therapeutic switch from biosimilar to originators and vice versa is concerned, at 3 month follow-up, a therapeutic change was necessary in 4 patients of each group. The changes in the biosimilar group were due to persistent anemia in 3 cases (increased dose in 2 cases and switch to epoetin beta in 1 case) and lowered dose after increased hemoglobin level in the fourth case. Three out of the four changes in the originator group were patients receiving darbepoetin alpha: they kept the same treatment with modified dosing regimen (1 from 40 mcg/week to 40 mcg/every 2 weeks, 1 started haemodialysis, and 1 experienced a dose reduction because of weight decrease). The fourth change was due to therapeutic ineffectiveness of epoetin alfa due to dose reduction.

At 6 month follow-up, 2 patients changed therapy in each group. The two changes in the originator group occurred in one case for increase in hemoglobin level and consequent dose reduction of epoetin beta and in the second case for ineffectiveness (with a therapeutic switch from darbepoetin alfa to epoetin alfa). The two changes in the group of biosimilar both occurred for increase in hemoglobin level and subsequent reduction of the dose of epoetin zeta. At 12 month follow-up, 3 patients in the biosimilar group and 1 in the originator group changed their therapy. In the biosimilar group, 2 patients increased the dose of epoetin zeta owing to decreased Hb level, and the third patient decreased the dose after increased Hb level. The case in the originator group had an increased dose of epoetin alfa owing to a decrease in the Hb level.

No ADRs were reported during the study period.

Discussion

To our knowledge, this is one of the few studies concerning comparative analysis of efficacy and safety of biosimilar erythropoiesis-stimulating agents vs originator based on data from daily clinical practice in patient with chronic kidney disease.

The number of patients was lower than that of other studies because of the exclusion and inclusion criteria applied and the low number of centers involved.

At enrollment, the two groups of patients were quite similar for number and gender distribution (p value = 0.708). The same is also true for initial weight and for all other baseline characteristics except hypertension.

A significant aspect to consider is that patients of the biosimilar group were in slightly worse health conditions as for their differences in the initial glomerular filtration rate and comorbidities. This finding may be surprising considering the skepticism about efficacy and safety of biosimilars.

The outstanding point of the study concerns the assessments of hemoglobin blood levels at baseline and at 3, 6, and 12 months follow-up. The values were similar between the two groups at baseline, while a higher significant increase (p value < 0.05) in the level of hemoglobin of patients treated with the biosimilar was detected at all follow-ups. Overall, these data denote a comparable efficacy of biosimilars. During the 12 months of the study, a steady increase in the Hb level in the biosimilar group was observed, whereas the other group experienced an initial increase followed by a slight decrease.

Therapeutic switches data are also being emphasized since in the biosimilars group switches were often caused by an increase in Hb level and, in addition, a higher number of patients with disease progression/worsening was detected at each follow-up in the originator group.

Therefore, biosimilars led to a better, or at least equal, outcome than originators despite the level of uncertainty in the analysis due to the limited patient numbers.

Several studies in the literature are in accordance with present results. Hörbrand et al. [5] compared the results of their study with others [6–9] and concluded that none of the results of those trials was in disagreement with the assumption that biosimilar and originator have similar efficacy and safety, also

for patients in chronic haemodialysis. As further evidence of the similar effectiveness of biosimilar and originator, Więcek et al. [10] have evaluated the therapeutic switching from originator to biosimilar or vice versa on Hb level, epoetin dose, and patient safety. That study revealed that both epoetins can be interchanged without any clinically significant alteration.

A Cochrane meta-analysis of 56 studies and 15,596 patients carried out by Palmer et al. [1] compared efficacy and safety of ESAs (originator and biosimilar ESAs) to treat anemia in adults with CKD. That meta-analysis concluded that there were no sufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data.

A study in a general population from Northern Italy by Ingrasciotta et al. [11] also showed no difference on Hb level between biosimilar and other ESAs, strengthening all the results previously discussed.

As for the safety profile of these drugs, no ADR were reported by the involved centers during our study.

The biological drugs require an additional monitoring paying particular attention to the ADR reporting. In addition, switching between different ESAs during the treatment might further affect the pharmacovigilance monitoring. An Italian study of Cutroneo et al. [12] analyzed ADR reports attributed to originator/biosimilar products in Italy during the period 2001–2013. Overall, 9601 ADR reports concerned biologicals, of which 298 reports regarded biosimilars. They concluded that a low proportion of ADR reports concerned biosimilars, which suggests a high rate of under-reporting.

An important limitation of ESAs and biological drugs remains the high cost and biosimilar use could lead to an important money saving for healthcare system. This saving may change from a country to another: France requires a compulsory price discount on biosimilars ranging between 10 and 20% of the reference drug price instead Italy and Norway use a progressive price discount model, which sets an initial price discount for a biosimilar that increases with the number of competitors. Belgium decided to apply an appropriate price discount ranging between 20 and 34% of the reference drug price [13].

The EU is the leading biosimilar market, but there are some challenges in this area that could improve use of biosimilars, such as the global harmonization of clinical data.

Other regulatory challenge is related to the interchangeability, i.e., the prescription of a biosimilar in place of the reference product. Recently, EU is considering biosimilars as "alternatives" to originators: this could allow an increase in the use of biosimilars that could be switched from the reference product either at the initiation or during the therapy through automatic drug substitution in pharmacy [14].

All observational studies have limits that interfere with the results, first of all, the small number of patients recruited. Moreover, the kind of patients selected is limited and highly specific and it is not a representative sample of the general population.

Moreover, observational studies could be influenced by a number of confounders such as population bias, disease severity, or other individual circumstances.

[15]. The initial health conditions represent one of the most significant confounding factors, depending on the severity of kidney disease in this case, one might expect a more or less effective response to treatment regardless of the type of drug administered. However, investigators are aware of these confounders and use statistical techniques to address them. For this reason, a propensity score adjustment analysis has been performed in order to address this issue: after adjusting for propensity score, differences in Hb increase among the treatment groups remain statistically significant at all time points; moreover, the significance increases—p values < 0.001 at each follow-up.

Conclusion

Our results have shown that originator and biosimilar ESAs are at least equally effective and safe for the treatment of anemia due to CKD. New strategies are necessary to improve market penetration of biosimilars, which may contribute to governing health care costs while keeping a high level of therapeutic efficacy. To date, the most important challenge should be the increase in confidence of authorities, clinicians, and patients in efficacy and safety of biosimilars that will lead to an increased use of biosimilar in clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest for the submitted work.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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