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REVIEW

Epoetin Biosimilars in Europe: Five Years On

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ABSTRACT

Biosimilars have been developed for several biologic therapeutic agents, including erythropoiesis-stimulating agents (ESAs). However, biosimilars cannot be assumed to be completely identical to the reference product, nor can two different biosimilars of the same reference product be considered equivalent. Accordingly, standards for approving biosimilars are distinct from those for generic versions of conventional pharmaceuticals.

By late 2007, two biosimilar epoetins (HX575 and SB309) had been approved by the European Medicines Agency (EMA), following a series of pharmacokinetic and pharmacodynamic equivalence studies, as well as phase 3 clinical comparability evaluations. Additionally, the results of a limited number of post-authorization interventional or observational studies and quality comparisons were published subsequently on both products.

The reported differences in glycosylation profiles between these epoetin biosimilars and their reference product, as well as the lack of long-term safety and efficacy evaluation, could indicate a need to develop a more comprehensive analysis of the available data, and to evaluate the post-authorization real-life data, in order to gain a better understanding of any potential implications of molecular structural or formulation differences on long-term safety and effectiveness.

Switching between an original reference ESA and a biosimilar (and possibly also switching between biosimilar versions of the same product) should be regarded as a change in clinical management. Clinicians need to be fully involved in such decisions. Prescribing by brand name will prevent unintentional substitution by pharmacists and allow for effective pharmacovigilance, in accordance with recent EU directives. In this review, the authors have

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analyzed most of the published information on the two epoetin biosimilars, HX575 and SB309, to highlight the points that healthcare providers may need to consider when assessing an epoetin biosimilar.

Keywords: Anemia; Bioequivalence; Biosimilars; Chronic kidney disease; Epoetins; Erythropoietins; Pharmacovigilance

INTRODUCTION

Since approval of the first recombinant human insulin in 1982, biologics have accounted for an increasing proportion of treatments approved by the European Medicines Agency (EMA) [1–2]. Recently, the patents for many biologics have expired [3], allowing manufacturers to produce alternatives, commonly referred to as "biosimilars" [3–4]. Table 1 lists the biosimilar erythropoietins currently licensed in Europe [5]. The introduction of biosimilar products is welcomed by the clinical community, as they may help to reduce drug expenditure and allow more patients access to high-cost therapies. Due to the complexity of manufacturing for biologic medicines, distinct regulatory pathways have been implemented.

The challenges for manufacturers and regulators posed by biosimilars are not straightforward, in contrast to the situation with conventional generic drugs. Manufacturers of biosimilars must conduct comparability studies to substantiate the similar nature of the new similar biological agent and its chosen authorized reference agent; EMA guidance states that the active substance of a similar biological medicinal product must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. Whether a specific product is considered similar is determined on a case-by-case basis. However, any differences between the similar biological agent and the reference agent also have to be justified by appropriate studies on a case-by-case basis.

It is known that recombinant epoetins made in different cell lines can differ in their carbohydrate structure, and this may affect their pharmacokinetics (PK) and potency [2, 6, 7]. In recognition of the potential impact of such differences, the World Health Organization (WHO) recommended assigning a different Greek letter identifier to distinguish epoetin drug substances differing in carbohydrate structure [8]. However, the interpretation of this rule with respect to biosimilar products has been voluntary on the part of the sponsor, with resulting inconsistency in its interpretation for biosimilar products approved in Europe.

Additionally, because the cells used to produce recombinant biologics usually release several isoforms, and since clinical efficacy depends on maintaining a specific 3-dimensional molecular structure, small differences or changes in any of

Table 1 Biosimilar epoetins currently licensed in Europe [5]

Molecule	INN	Brand name
HX575	Epoetin alfa	Abseamed® (Medice Arzneimittel Putter, Iserlohn, Germany) Binocrit® (Sandoz GmbH, Kundl, Austria) Epoetin alfa Hexal® (Hexal Biotech, Holkirchen, Germany)
SB309	Epoetin zeta	Retacrit® (Hospira, Lake Forest, IL, USA) Silapro® (Stada, Bad Vilbel, Germany)

INN international nonproprietary name

the manufacturing steps for recombinants could subsequently change that structure [4]. The increase in the number of pure red cell aplasia (PRCA) cases among patients with chronic kidney disease (CKD) who were given a reformulation of an epoetin product exemplifies the potential for seemingly small changes in biopharmaceutical production to induce rare but potentially serious adverse events [9]. It also underscores the importance of long-term follow-up and effective pharmacovigilance [10–11].

Almost 5 years after the introduction of the first biosimilar epoetin in Europe, this article focuses on reviewing the registrational clinical studies and key post-marketing studies conducted in support of the currently available epoetin biosimilars, HX575 and SB309. Rather than providing a critique of HX575 and SB309, the article aims to discuss present experience with epoetin biosimilars, based on currently published data, and the points that could be considered by regulatory bodies, pharmacists, and clinicians.

METHODS

A systematic search was not conducted. An initial search using the terms "biosimilars," "epoetins," "epoetin alfa," "epoetin zeta," "epoetin theta," "Binocrit," and "Retacrit" was conducted on PubMed, and additional material was retrieved from the websites of regulatory authorities (EMA, WHO, etc.). Further references were identified from the reference lists of the publications that were retrieved.

REGULATORY APPROVAL OF BIOSIMILARS

As opposed to the situation with generic drugs, where manufacturers are required to conduct only PK studies, the Committee for Medicinal Products for Human Use (CHMP) had issued guidance covering the general requirements for clinical studies of biosimilars and individual requirements for each protein [12]. This reflects a long-standing recognition among European Union (EU) regulators that the generics approach is not appropriate for biologics. Within the EU, in addition to demonstrating biophysical similarity, it is obligatory that manufacturers provide sufficient nonclinical (in vitro studies and in vivo PK, pharmacodynamic [PD], and toxicological studies) and clinical data to demonstrate clinical similarity/therapeutic equivalence to the reference agent [10]. The approval of biosimilar epoetins for treatment of renal anemia previously required at least two confirmatory efficacy studies in patients with CKD, including one correction phase study using subcutaneous (SC) administration in epoetin-naïve patients and one maintenance study using intravenous (IV) administration in patients previously treated with epoetins. Revised guidelines released in 2010 allowed an alternative approach of showing comparable efficacy for one route of administration (reasonably, the SC route, to provide the mandatory comparative immunogenicity data) in a comparative clinical trial and providing comparative single dose and multiple dose PK/PD bridging data for the other route of administration [13].

If the biosimilar epoetin sponsor seeks a label with multiple indications, it is possible that approval may be granted based on a single efficacy study in a single appropriate indication [10]. The rationale for this is that the mechanism of action of epoetin is the same for all currently approved indications and there is only one known epoetin receptor. Thus, demonstrating efficacy and safety in one indication, for example, in renal anemia, may allow the manufacturer to extrapolate the results to the originators' other indications that use the same route of administration [13].

This situation applies to all biosimilar applications, not just that for epoetin. For example, the chemotherapy-induced anemia indication for all epoetin biosimilars was granted by extrapolation of data [13].

Design of Therapeutic Equivalence Studies for Biosimilar Epoetins

A trial that aims to show therapeutic equivalence of epoetins requires the pre-specification of a clinically accepted margin for the differences between treated groups. A careful assessment and a clinical rationale are, therefore, needed to define the accepted margin appropriately. The CHMP recommends that each therapeutic equivalence study for biosimilar epoetins has two pre-specified co-primary endpoints: change in hemoglobin and change in average dose [12]. Thus, a biosimilar can be approved based on therapeutic equivalence on both primary endpoints, as shown by two-sided confidence intervals (CIs) for between-group differences being within pre-specified margins. However, these recommendations have evolved following the advent of biosimilars and some equivalence studies preceded their introduction.

CLINICAL DATA AND ISSUES FOR SPECIFIC BIOSIMILAR EPOETINS

HX575

Substance HX575 (Rentschler Biotechnologie, Laupheim, Germany) was approved by the EMA in late 2007 and has been marketed since then as Binocrit® by Sandoz (Sandoz GmbH, Kundl, Austria), as epoetin alfa Hexal® by Hexal Biotech (Holkirchen, Germany; another Novartis subsidiary) and as Abseamad® by Medice Arzneimittel Putter (Iserlohn, Germany; a Sandoz licensing partner) [14].

HX575 has the same amino acid sequence as the reference product (Eprex®, Erypo®, Janssen-Cilag, New York, NY, USA), but has a greater number of phosphorylated high mannose-6-phosphate (M6P) glycans, and lower levels of N-glycolylneuraminic acid and diacetylated neuraminic acids [15–16]. Despite the WHO recommendations to assign a different Greek suffix for each recombinant epoetin, HX575 is using the same international nonproprietary name (INN) of epoetin alfa [8].

Clinical Pharmacology

The pivotal IV PK/PD study compared HX575 and epoetin alfa (both 100 IU/kg) three-times weekly for 4 weeks. The study enrolled 80 healthy men and the primary endpoint for PK was area under the curve (AUC) for epoetin concentration, while the primary endpoint for PD was the area under the effect curve for hemoglobin ($AUEC_{Hb}$). The two products could be considered pharmacokinetically bioequivalent if the 90% CIs of HX575 epoetin AUC were within 80–125% of the reference product, and pharmacodynamically bioequivalent if the 90% CI for the $AUEC_{Hb}$ ratio was within 96.8–103.2% [17].

Based on the $AUEC_{Hb}$ ratio and 90% CI (99.9% [98.5–101.2%]), the hematopoietic profiles of HX575 and epoetin alfa were similar. The two products were deemed equivalent. However, after only a single IV dose, some PK differences were noted, as demonstrated by the 18% lower $AUC_{0\text{-}12h}$ after HX575 versus epoetin alfa administration; geometric mean (geometric mean coefficient of variation) 8,098 mIU/mL*h (44.5%) after HX575 versus 9,903 mIU/mL*h (33.3%) after epoetin alfa. Although HX575 was considered pharmacokinetically equivalent to epoetin alfa following multiple IV administrations, at steady state, the $AUC_{0\text{-}36h}$ was approximately 10% lower after HX575 than after epoetin alfa; geometric

mean (geometric mean coefficient of variation) 8,153 mIU/mL*h (25.4%) for HX575 versus 9,036 mIU/mL*h (21.1%) for epoetin alfa [17].

The 10% reduction in exposure, as assessed by changes in HX575 AUC observed in this study, together with the more complicated manufacturing process of biopharmaceuticals, further supports EMA guidance that PK profile alone is insufficient to support the similar efficacy and safety of two biotechnology-derived medicinal products [12]. In clinical practice, a reduction in exposure could translate into a change in clinical response due to significant fluctuation in erythropoietin therapeutic levels [17]. Therefore, clinicians may need to monitor hemoglobin levels and modify the dose of HX575 after switching patients who are stable on epoetin alfa.

Another PK study compared SC HX575 and epoetin beta, finding that the AUC of HX575 was also approximately 10% lower than the comparator, whereas the maximum serum concentration (C_{max}) differed by only 3%. However, these findings have limited relevance [18], since epoetin alfa was not used as a reference [15].

Safety and Efficacy

One maintenance study in clinically stable adult dialysis patients was conducted with HX575. A total of 478 patients received HX575 (n = 314) or epoetin alfa (n = 164) for 28 weeks, followed by HX575 until week 56. HX575 and epoetin alfa were considered to be clinically equivalent if the 95% CI of the hemoglobin difference was within the pre-specified equivalence limit (0.5 g/dL) [19]. Based on this criterion, HX575 was deemed equivalent to epoetin alfa. The hemoglobin difference was 0.084 g/dL (95% CI –0.170 to 0.338). The mean baseline epoetin dosages were 7,054 IU/week in the HX575 group and 6,623 IU/week for epoetin alfa. The least square mean absolute dose changes were –469.9 (±148.8) and –642.2 (±181.5) IU/week, respectively. Thus, from baseline (weeks –2 to 0) to evaluation (weeks 25–28), patients receiving epoetin alfa experienced dose reductions of 7.4%, while patients receiving HX575 had dose reductions of 3.8%. As no pre-specified equivalence margin for this relative dose change was given, it is difficult to determine whether these differences are potentially clinically meaningful or indicate that a greater dose of HX575 is required for similar clinical response. Moreover, factors such as batch-to-batch variations cannot be excluded [19]. In this maintenance IV study, no significant differences in patterns of adverse events were noted and no patient showed signs of PRCA [19].

As part of post-authorization risk management plans required by the EMA, an open-label, prospective single-arm study was conducted on more than 1,500 patients with CKD [20]. HX575 was given via the IV route, mainly to assess its long-term safety profile, while efficacy was a secondary outcome. Safety was assessed in the full patient population and was reported to be in line with expectations, with no patient developing PRCA. The efficacy results for hemoglobin and epoetin dosing showed maintenance of hemoglobin within levels of 11.2–11.3 g/dL following conversion from other erythropoiesis-stimulating agents (ESAs). Analysis of the data on hemoglobin and ESA dosing was restricted to the per-protocol dataset, which excluded almost 33% of the patient population [20].

HX575 is currently indicated only for IV use in hemodialysis patients, reflecting the lack of a successfully completed comparator trial with the SC route. An attempted label extension study for this route of administration was terminated due to unexpected safety findings (PRCA), the potential relevance of which is discussed later in this review [21, 22].

While these results suggest that HX575 is well tolerated and effective, some issues remain

unresolved, particularly whether differences in glycosylation and epoetin exposure are clinically meaningful [3, 7, 9, 21]. One further trial has also raised the prospect of a difference in potency, depending on the manufacturing production site [23]. This study compared HX575 and other registered epoetin alfa products over 4 weeks of treatment. Healthy subjects (n = 268) were randomized to receive HX575 or Epogen® (Amgen Inc, Thousand Oaks, CA, USA). Both agents were found to be bioequivalent, though HX575 exposure was shown to be approximately 10% lower [23]. The study then compared HX575TT, which was manufactured at a different site from HX575, with Eprex/Erypo. The epoetins produced comparable PD responses; however, the AUC of HX575TT was 15% higher than that of HX575, suggesting that the potency of HX575 may differ depending on the production site [23]. Additionally, the manufacturers did not prospectively define the PK acceptance range in registration trials and the AUC after IV treatment was outside the post-hoc range [3].

SB309

SB309 (Norbitec, Uetersen, Germany) was the second epoetin biosimilar to receive EMA approval. With the INN of epoetin zeta, it has been traded subsequently as Silapo® by Stada (Bad Vilbel, Germany) and as Retacrit® by Hospira (Lake Forest, IL, USA). The protein backbone of SB309 is similar to that of epoetin alfa, but it contains a slightly higher amount of glycoforms without an O-glycan chain. The amounts of undesired N-glycolyl and acetylated forms of neuraminic acid are higher in epoetin alfa than SB309 [16, 24]. There are, however, no known clinical consequences of the presence of the variants of neuraminic acid at the levels that are present in these products [25].

Clinical Pharmacology

Several clinical trials have studied the PK and PD of SB309. The first trial compared the bioavailability of SB309 and epoetin alfa following a single IV dose (n = 21). The 90% CI for C_{max} was within the acceptance ranges, which were defined post-hoc. The 90% CI for AUC fell within these acceptance ranges after the application of a correction factor allowing for differences in protein content. After applying the correction factor, the bioavailability of SB309 was reported to be 0.93 (0.89, 0.97) [24, 26].

A second trial examined the bioavailability of SC versus IV SB309 and compared the PK characteristics of SB309 and epoetin alfa after a single SC dose in healthy volunteers (n = 48). The study results (primary analysis) suggested sub-availability of SB309 versus epoetin alfa [27]. The 90% CIs for AUC and C_{max} were within the post-hoc defined ranges, after applying the correction factor [24]. Some authors have suggested that the lower bioavailability of SB309 in both studies reflected the greater protein content of epoetin alfa [24, 26, 27].

Safety and Efficacy

The safety and efficacy of SB309 have been studied in three clinical trials. Two of these investigated IV use, either for correction of anemia or as maintenance therapy [28, 29]. In the correction phase study, patients were randomized to treatment with SB309 (n = 305) or epoetin alfa (n = 304) for 24 weeks [28]. The mean (± standard deviation [SD]) hemoglobin level over the final 4 weeks of treatment was 11.61±1.27 g/dL for the patients treated with SB309 versus 11.63±1.37 g/dL for patients treated with epoetin alpha, which was within the pre-defined equivalence range. The mean (±SD) weekly dosage of epoetin per kg body weight during the last 4 weeks of treatment

was approximately 10% higher with SB309 compared with epoetin alfa (182.20±118.11 vs. 166.14±109.85 IU/kg/week) [28]. A correction factor was used to reanalyze original data with respect to dosage, in order to correct for the higher protein content noted in epoetin alfa compared to SB309 [24]. Despite this, the correction phase study failed to meet its pre-specified criteria for equivalence of ±14 IU/kg/week (95% CI –23.5 to 17.48 IU/kg/week). However, the 95% CI were within a modified post-hoc acceptance range of ±45 IU/kg/week [24, 28].

The maintenance study enrolled 313 hemodialysis patients with renal anemia who had received epoetin for ≥3 months [29]. Patients were randomized to receive one epoetin product for 12 weeks and then the other for an additional 12 weeks in a crossover design study. Each epoetin was given IV three times per week over a 12-week treatment period [29]. Mean hemoglobin levels were 11.35 g/dL (range: 8.96–14.22 g/dL) and 11.54 g/dL (range: 8.7–13.84 g/dL) for SB309 and epoetin alfa, respectively. The 95% CIs of the intraindividual differences in hemoglobin levels (0.09–0.28 g/dL) were within the pre-defined ranges [29]. Switching from epoetin alfa to SB309 increased the dose required by approximately 10–15% and transiently decreased the hemoglobin level by approximately 5%. Switching from SB309 to epoetin alfa reduced the dose required by around 10% and increased hemoglobin levels by approximately 10% [24, 29]. As in the correction phase study, a correction factor was introduced to correct for differences in protein content of the two ESAs being compared. In the maintenance phase study, this led to a widening of the revised 95% CI for dosage of 3.086–13.917 IU/kg/week. Again, the 95% CIs were within the modified acceptance range of ±45 IU/kg/week [24, 29].

One weakness of this study was that the 12-week treatment period for each epoetin would not have allowed enough time for dose titration of hemoglobin values back to baseline levels. In a crossover study of this design, longer treatment periods would have allowed a better comparison of the dose required to maintain consistent hemoglobin levels. In addition, mean hemoglobin levels and epoetin doses were calculated over the whole 12-week period instead of waiting until any overlapping effects of the ESAs were over.

The long-term safety of IV SB309 during maintenance of target hemoglobin in patients with anemia receiving chronic hemodialysis has been reported [30]. Combined outcomes from 745 patients who completed double-blind treatment during the two earlier efficacy trials were analyzed [28, 29]. Patients received SB309 for 56 weeks or 108 weeks to maintain individually determined, stable hemoglobin values between 10.5–12.5 g/dL with constant epoetin dosages. Although 213 patients withdrew during the first 56 weeks due to adverse events, noncompliance, and other factors, SB309 maintained hemoglobin levels within the target range at a constant dose. Infections and infestations (34% of patients treated with SB309) emerged as the most common adverse event. Two patients expressed anti-epoetin antibodies; however, these were present at screening for the preceding trial. Approximately 5% of adverse events were considered to be related to the study treatment. Almost 100% of patients and investigators reported tolerability as excellent or good, and most adverse events that were possibly related to study treatment were consistent with those previously reported with ESAs [30].

A further post-hoc analysis of the two 24-week, randomized, double-blind correction and maintenance studies and the 56-week, open-label, follow-on study reported above evaluated the impact of switching hemodialysis patients with CKD between epoetin alfa and SB309 on

hemoglobin concentration, epoetin dose, and safety [28–31].

In the maintenance study, 118 patients switched from epoetin alfa to SB309 and 121 switched from SB309 to epoetin alfa; 104 of the 121 patients switched back to SB309. Only 101 patients completed 12 weeks of follow-up treatment without apparent major protocol deviations. In the correction study, 249 of 268 patients switched from epoetin alfa to SB309. A total of 242 patients completed 12 weeks of follow-on treatment without any apparent major protocol deviations. Therapies were considered equivalent if the 95% CI of the mean intraindividual difference in hemoglobin concentration before and after the switch remained within the pre-specified equivalence limits (±1.0 g/dL) [31].

Hemoglobin levels were considered to be maintained if the mean level remained within the target range (10.5–12.5 g/dL) 8–12 weeks after the switch. Mean differences in hemoglobin and 95% CIs following the switch remained within pre-specified equivalence ±1.0 g/dL limits (10.94±0.84 g/dL for SB309 vs. 11.02±0.94 g/dL for epoetin alfa at 12 weeks); however, this range is wider than the 0.50–0.75 g/dL ranges used in other epoetin comparative studies. The 95% CIs of the mean difference in weekly epoetin dose stayed within modified equivalence margins. The incidence and nature of treatment-emergent and serious adverse events was similar among all groups and was unaffected by the ESA switch. It was reported that no patient developed anti-epoetin antibodies or PRCA during the study [31].

The safety and efficacy of SC SB309 and epoetin alfa have also been compared in patients with renal anemia undergoing chronic hemodialysis [32]. In a maintenance study, patients received SB309 (n = 232) or epoetin alfa (n = 230) for 28 weeks after an open run-in period of 12–16 weeks, during which time the dose of epoetin was adjusted. Mean (±SD) hemoglobin concentrations during the last 4 weeks were 10.94±0.84 g/dL with SB309 and 11.02±0.94 g/dL with epoetin alfa, while the mean (±SD) weekly epoetin doses were 97.0±94.3 and 86.0±78.0 IU/kg/week, respectively. The 95% CI of the difference in mean hemoglobin level (–0.28 to 0.12 g/dL) and dose (–8.06 to 29.96 IU/kg/week) was within the 45 IU/kg/week equivalence range [32]. In this study it was reported that there were no differences in tolerability between treatment groups, and no patient developed anti-epoetin antibodies or clinical signs of PRCA. Nevertheless, the dropout rate was relatively high, with 72 patients (15.6% of the randomized population [n = 462]) withdrawing [32].

IMMUNOGENICITY RISK

Immunogenicity is one of the most important potential adverse drug reactions that might be associated with the use of biologics, with PRCA offering a striking, albeit rare, example of a serious adverse event [10, 33]. Many cases of immunogenicity are asymptomatic; for example, patients taking recombinant human insulin develop antibodies without clinical consequences [33]. Nevertheless, the production of antibodies against an endogenous protein may undermine therapeutic efficacy, induce autoimmunity to endogenous molecules, or produce systemic immune reactions [2]. Immunogenicity can arise from minor changes in manufacturing and may emerge early or only after long-term exposure [33, 34], underscoring the need for effective pharmacovigilance.

None of the pre-registration IV epoetin biosimilar studies reported the presence of neutralizing anti-epoetin antibodies, or any signs and symptoms consistent with immune-mediated PRCA, although it should be noted that small numbers of subjects were enrolled

into the studies and the duration of treatment was relatively short.

The recent early cessation of the Study to Evaluate the Efficacy, Safety and Immunogenicity of Subcutaneous HX575 in the Treatment of Anemia Associated with Chronic Kidney Disease (SWEEP) could also reflect the importance of understanding and evaluating the potential immunogenic implications of any minor differences in manufacturing or packaging of biologics. SWEEP randomized 337 pre-dialysis patients who had not previously taken ESAs to receive either HX575 or Erypo [21]. Two patients in the HX575 arm developed neutralizing anti-epoetin antibodies; bone marrow biopsy confirmed PRCA in one patient, while the other patient died from myocardial infarction before a biopsy could be conducted [21]. The probability of this observation should be put into context of the background level of PRCA for other ESAs approved for the SC route. Published pharmacovigilance data suggest the background rate of PRCA for epoetin beta, darbepoetin alfa, and epoetin alfa prior to the formulation change was approximately 1 in 100,000 patient-years [35, 36]. Prevalence of PRCA during previously reported clusters approached 5/10,000 patient-years for Eprex and 1/2,608 patient-years for certain ESAs in Thailand [37–38]. In this context, the SWEEP trial would not have been expected to detect any incidence of neutralizing antibodies and this finding highlights the importance of clinical evaluation, even if events are expected to be rare and the study should not have sufficient power for detection. A recently published root cause analysis suggested that contamination by tungsten during manufacturing of the syringes used for primary packaging, leading to protein denaturation and aggregation of HX575 batches, might have been responsible for the higher immunogenicity reported in this study [22]. HX575 has not received EMA authorization for a label revision permitting the SC route of administration in CKD patients not on dialysis, because of this unexpected finding.

In conclusion, the immunogenicity risk associated with biosimilar epoetins cannot be excluded. Notwithstanding the unexpected finding of anti-erythropoietin-neutralizing antibodies in the SWEEP study for HX575 [21, 22], only long-term clinical experience involving a relatively large number of patients, in conjunction with careful pharmacovigilance, will provide more robust information.

DISCUSSION

Biologics are likely to remain among the most clinically successful therapeutic agents. It has been almost 5 years since biosimilar epoetins first became available. The evidence summarized here supports the view expressed by others that prescribers should be aware of the clinical considerations associated with switching between reference products and biosimilars [2, 10, 11, 34]. Certainly, similar PK profiles alone do not support the assumption of similar efficacy and safety of two biotechnology-derived medicinal products.

While it was reported that several studies met the bioequivalence endpoints required by the EMA between a biosimilar epoetin and the reference agent, many of these trials had limitations in terms of study design and execution. Equivalence margins need to be better defined and adhered to when designing clinical studies. Currently, while target ranges for hemoglobin levels are routinely set and adhered to in the studies seeking to prove biosimilarity between ESAs, epoetin dose ranges are either not being set, are being set inappropriately, or are not being adhered to. For example, in registration trials, the dosing acceptance range

for SB309 was pre-defined but not met and a post-hoc correction factor in the maintenance study was required to bring the parameters within the range [29]. Despite this, the dosage of SB309 was approximately 10% higher than that for epoetin alfa.

The studies reviewed in this paper highlight other clinical considerations. For example, the finding that the AUC for HX575TT was 15% higher than that of HX575 [23] may suggest that potency depends on the production site. Additionally, the epoetin products may have some differences in formulation and glycosylation patterns, and potential effects on potency cannot be excluded. The unexpected rate of neutralizing antibodies and the PRCA reported in the SWEEP study with SC HX575 [21] emphasize the potential uncertainties and need for further understanding of the potential differences in immunogenic profiles between biosimilars and originators. While it has been suggested that tungsten-related aggregation of HX575 batches could have been responsible for differences in the immunologic responses seen in SWEEP, as tungsten has also been found in other ESAs, this potential association may need to be investigated further [22].

Studies of currently licensed biosimilar epoetins showed a varying degree of glycosylation compared with the reference drug. For example, HX575 (Binocrit) has a higher M6P content (40%) compared with the reference epoetin. Glycosylation plays several roles in the biological properties and effects of therapeutic proteins, potentially impacting protein folding and trafficking, ligand recognition and binding, biological activity, stability, pharmacokinetics, and immunogenicity. Thus, when evaluating a biosimilar epoetin, it may be essential to assess the impact of differences in carbohydrate content on all of these properties. Additionally, the potential impact of batch-to-batch variations in both biosimilar epoetins and reference products may need to be considered. Since small changes in the manufacturing process could have an unexpected impact on the clinical outcome of follow-on biosimilars, tests for consistency in manufacturing processes are critical in assessment of any biological product. Moreover, as biological products are very sensitive to environmental factors, such as light and temperature, stability testing should be conducted using study designs that are able to account for these environmental factors.

The execution of long-term post-marketing safety studies and appropriate risk management plans will be crucial in generating a better understanding of the long-term safety profiles of recently approved biosimilar epoetins.

Some points for clinicians to consider are summarized in Table 2. A switch between the

Table 2 Points for the clinician to consider

- Pre-registration clinical trials, study design, sample size
- Study population and how representative it is of the clinical population
- Study duration, statistical methodology
- Difference between the trial and reference drug (biologic activity, route of administration, median dosage, and endpoint
- The need to establish local protocols/care bundles to avoid inadvertent drug interchange, or switching administration route (IV vs. SC)
- Safety, adverse events, potential for immunogenicity
- Post-marketing data, clinical experience, adverse event reporting

IV intravenous, *SC* subcutaneous

reference product and the biosimilar may be considered "as a change in clinical management," as advocated by Mellstedt and colleagues [4]. Arguably, the same applies to switching between biosimilar versions of the same reference product. If clinicians wish to ensure that a given patient receives a specific biologic or biosimilar, they should prescribe by brand name to prevent unintentional substitution by pharmacists and allow for effective pharmacovigilance. This approach has been highly recommended in guidelines and legislation released in different EU countries, advocating the avoidance of automatic substitution [10].

In recognition of the need for special requirements for effective pharmacovigilance for biologics, new pharmacovigilance legislation came into effect across the EU in July 2012 [39]. This legislation requires that for all adverse drug reaction reports, all appropriate measures should be taken to identify the brand name and batch number of the product concerned. Recent EMA guidance has reaffirmed the fundamental differences between biosimilar and generic medicines, and acknowledged the importance of the patient and physician in prescribing/switching decisions, recommending that "for questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist" [40].

CONCLUSION

Although considered therapeutically equivalent by the EMA, the registration studies for HX575 and SB309 reviewed here suggest that differences in their PK and dosing properties exist. The CHMP strongly recommends that each confirmatory study for biosimilar epoetins has two co-primary endpoints – change in hemoglobin and change in average dose – and that a biosimilar is approved based on therapeutic equivalence on both primary endpoints, assessed by CIs for between-group differences that lie within pre-specified margins. Such co-primary endpoints appear to have not been included when some biosimilar studies were undertaken. As differences do exist between biosimilars, both in terms of their means of manufacturing and glycosylation profiles, long-term safety and tolerability should continue to be monitored. Automatic substitution of biological medicines is not encouraged and clinicians should be fully involved when a switch between originator products and biosimilars is considered. Additionally, appropriate pharmacovigilance measures should be put in place to ensure that adverse events are attributed to the responsible biological medicine.

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