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FULL REVIEW

The ESA scenario gets complex: from biosimilar epoetins to activin traps

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ABSTRACT

Recombinant human erythropoietin (rhEpo, epoetin) has proved beneficial in preventing transfusion-dependent anaemia in patients with chronic kidney disease. Apart from copied epoetins distributed in less regulated markets, 'biosimilar' epoetins have gained currency in many regions, where they compete with the originals and with rhEpo analogues with prolonged survival in circulation ('biobetter'). Recombinant erythropoiesis stimulating agents are potent and well tolerated. However, their production is costly, and they must be administered by the parenteral route. Hence, other anti-anaemia treatments are being evaluated. Clinical trials are being performed with stabilizers of the hypoxia-inducible transcription factors (HIFs), which increase endogenous Epo production. HIF stabilizers are chemical drugs and they are active on oral administration. However, there is fear that they may promote tumour growth. Epo mimetic peptides have also raised expectations. Yet the prototype peginesatide was recalled after just 1 year of its widespread use in the USA because of serious side-effects including cases of death. Most recently, clinical trials have been initiated with sotatercept, a recombinant soluble activin receptor type 2A IgG-Fc fusion protein. Sotatercept binds distinct members of the transforming growth factor-β family, thereby preventing the inhibitory action of these factors in erythropoiesis. Taken together, rhEpo and its long-acting recombinant analogues will likely remain mainstay of anti-anaemia therapies in the near future.

Keywords: activin, anaemia, biosimilars, chronic kidney disease, erythropoiesis-stimulating agents

INTRODUCTION

Erythropoietin (Epo) is essential for the growth of colony-forming units-erythroid (CFU-Es) and other erythrocytic progenitors. Insufficient Epo production contributes to the anaemia associated with chronic kidney disease (CKD). Treatment with erythropoiesis-stimulating agents (ESAs) can reduce the requirements for red blood cell (RBC) transfusion. Recombinant human Epo (rhEpo, epoetin) has been applied in the renal setting for over 25 years. Recently, copy versions of epoetins have received marketing authorization in many regions, including the European Union (EU). In addition, second-generation rhEpos with improved pharmacokinetic properties have become therapeutic options.

The administration of rhEpo and its analogues is effective and rarely associated with serious adverse events (SAEs). However, recombinant ESAs are expensive and they require a parenteral route of administration. Hence, alternative

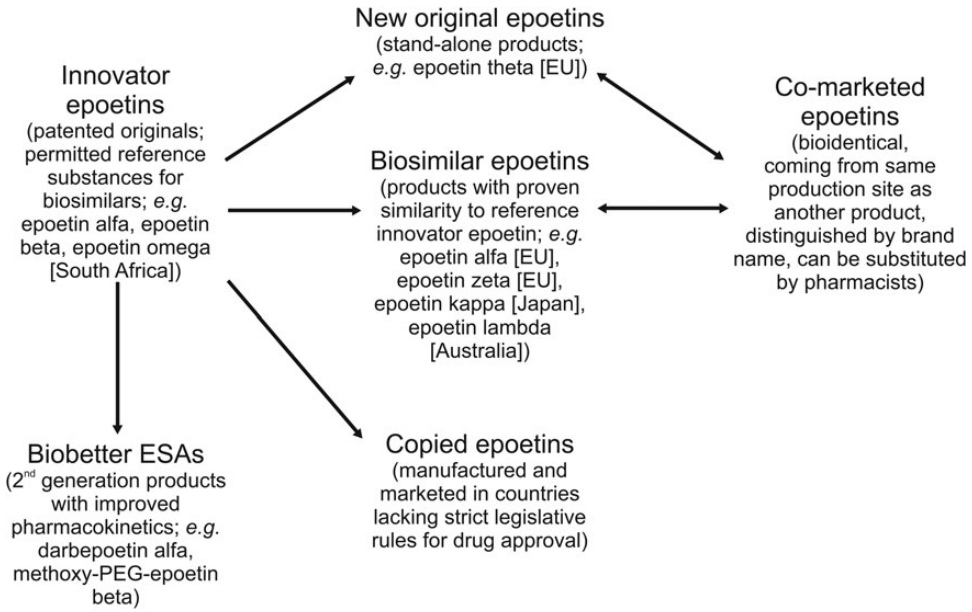

FIGURE 1: Types of recombinant ESAs.

therapeutics have been designed for clinical testing: (i) small molecule drugs that stabilize hypoxia-inducible factors (HIF) and promote Epo production, (ii) synthetic Epo mimetics that signal through the Epo receptor (Epo-R) and (iii) recombinant proteins that stimulate erythrocytic progenitors independent of the Epo-R. The present article critically reviews the pharmacology of the various ESAs.

RECOMBINANT HUMAN ERYTHROPOIETINS

Original epoetins

First there were two innovator rhEpos (Figure 1). Epoetin alfa has been traded primarily under the brand names Epogen® (Amgen, Inc.), Procrit® (Janssen Products, LP) and —outside the USA—Eprex® (or Erypo®; Ortho Biotech) and Espo® (Kirin) [1]. Epoetin beta has been traded primarily under the brand names NeoRecormon® (F. Hoffmann-LaRoche) and Epogin® (Chugai). In retrospect, it appears that physicians considered the two epoetins interchangeable (meaning the practice of switching one for the other) and used them for the same major indications (anaemia associated with CKD or with myelosuppressive chemotherapy). Nonetheless, every epoetin is distinct with respect to its glycosylation pattern, despite the identical peptide core of the 165 amino acids [2]. Therefore, the epoetins received the qualifying Greek letter suffixes (e.g. epoetin alfa versus epoetin beta) in following the international non-proprietary name (INN) policy of the WHO [3]. Of note, however, the carbohydrate portions of biopharmaceutical glycoproteins will usually vary over time, due to manufacturing process changes [4].

In 2009 epoetin theta received EU marketing authorization as a stand-alone drug, with the brand names Biopoin® (CT Arzneimittel/Teva) and Eporatio® (Ratiopharm/Teva), which are co-marketed identical medicines (Figure 1). Despite using epoetin beta as a comparator, epoetin theta is not a biosimilar (http://www.ema.europa.eu). Stand-alone (or 'full') new drug applications are supported entirely by product-specific results of the applicant. Superior pharmacological properties of epoetin theta over the other epoetins have not been described.

BIOSIMILAR EPOETINS

To obtain EU marketing authorization for a biosimilar epoetin, comparative quality studies with an approved reference epoetin, and non-clinical and clinical safety and efficacy studies are required. Two biosimilar epoetins (substances HX575 and SB309) proved sufficient analogy to the innovator epoetin alfa (Eprex®/Erypo®) in preclinical and clinical studies according to the EU guidelines (http://www.ema.europa.eu). As noted above, according to the WHO [3], glycosylated biologicals should be given a qualifying Greek letter suffix, and only biosimilars containing non-glycosylated biologicals (e.g. filgrastim or somatropin) should receive the same INN as the reference drug. Nevertheless, the substance HX575 has received the INN 'epoetin alfa', although its glycosylation pattern differs from that of the reference epoetin alfa (Eprex®/Erypo®). HX575 has been approved under three different trade names: Binocrit® (Sandoz), Epoetin alfa Hexal® (Hexal Biotech) and Abseamed® (Medice Arzneimittel Putter). These co-marketed medicines are produced by use of the same expression system and firm (Figure 1). Thus, they are true 'bioidenticals' which may be substituted among themselves (substitution is typically performed at hospital or retail pharmacies). The other biosimilar, substance SB309, has received the INN 'epoetin zeta'. It is marketed under two different trade names in the EU: Silapo® (Stada) and Retacrit® (Hospira), which are bioidenticals among themselves.

Note that the naming of the various epoetins can differ between regions. The Australian Therapeutic Goods

Administration (TGA) has given the INN 'epoetin lambda' (Novicrit®, Novartis Pharm, Australia) to the biosimilar having the INN 'epoetin alfa' in the EU. Since 2010, an 'epoetin kappa' has been available in Japan, which was approved as a biosimilar to epoetin alfa. However, on isoelectric focusing, the isoform bands of epoetin kappa expand more widely towards the basic area, and the profile is composed of at least eight bands, which differs greatly from the profile of other epoetins [5].

Extrapolation of indications is another critical issue. The European Medicines Agency (EMA) has stated that 'since the mechanism of action of epoetin is the same for all currently approved indications and there is only one known epoetin receptor, demonstration of efficacy and safety in renal anaemia will allow extrapolation to other indications of the reference medicinal product with the same route of administration' [6]. Thus, the biosimilar epoetins have received marketing authorization not only for i.v. administration in adult CKD patients on haemodialysis. Marketing authorization has been granted also for i.v. administration in adult CKD patients on peritoneal dialysis or not yet undergoing dialysis (SB309 has been also approved for s.c. administration), in paediatric CKD patients on haemodialysis, furthermore i.v. or s.c. administration in adults receiving chemotherapy for malignancies, patients prior to major elective orthopaedic surgery (only HX575) and patients on an autologous blood donation programme (only SB309), although no controlled trials were performed for approval with respect to the latter indications. A position paper from the Italian Society of Haematology, Italian Society of Experimental Haematology and Italian Group for Bone Marrow Transplantation has stated that 'this use presents a clinical dilemma' because of concerns that 'unexpected toxicity might have a detrimental effect in non-anaemic individuals administered high doses of epoetin to support blood donation as a preventive measure' [7]. In this author's mind, extrapolation should be indicated in the products' labels to provide information for physicians, pharmacists and patients, which applications were conducted without own data, i.e. by extrapolation from reports of the original manufacturer.

Within their approved indication profile all epoetins are interchangeable, based on the decision of a physician. However, because biosimilars—unlike generic drugs—are not identically equal to the original, automatic substitution at the pharmacy is prohibited in most EU countries. Pharmacists can only substitute bioidentical epoetins (=co-marketed medicines containing identical drug substances). For safety reasons, physicians should prescribe epoetins by using brand names to enable pharmacovigilance testing and to ensure that adverse events are assigned to the responsible product. Clearly, arbitrary product changes ('product hopping') should be avoided.

Copied epoetins from less controlled regions

Copied biopharmaceuticals have been used for many years in countries with less strictly controlled marketing regulations, including parts of Latin America, Asia, Africa and non-EU Europe. Overall, ~80 different commercial epoetins (mostly with the INN epoetin alfa) were globally counted a few years ago [8]. Many of these products present with unusual glycosylation patterns and abnormal *in vivo* bioactivities [9]. In fact, covalent aggregates were detected in some brands [10]. Aggregated protein could have been the reason for the high prevalence (1 out of 2608 patients) of anti-Epo antibodies (Abs)-induced pure red cell aplasia (PRCA) in Thailand [11]. In that publication, it is noted that the afflicted patients were treated with 'biosimilar' epoetins [11]. The present author wishes to contradict this diction. For the sake of clarity, the term 'biosimilar' should be used only for biopharmaceuticals that were approved on a strict regulatory pathway (e.g. by EMA, TGA, FDA etc.), and not for copied products available in countries with a less controlled market [12]. Note that the incidence of anti-Epo Abs-induced PRCA is very low (<0.03 per 10 000 patient years) on use of any of the epoetins that are approved in developed countries [13].

Second-generation epoetins

Recombinant ESAs with prolonged survival in circulation allow for less frequent administration (='biobetter'). Darbepoetin alfa (Aranesp®; Amgen) is a mutated hyperglycosylated analogue of rhEpo, containing two additional N-linked glycans in positions 30 and 88 [14]. The plasma half-life of darbepoetin alfa is 24–26 h, compared with 4–10 h with regular epoetins [1]. Darbepoetin alfa is effective in CKD patients, when administered once every 2 weeks or monthly. According to a long-term crossover study in Japan darbepoetin alfa is more potent than epoetin in reducing levels of hepcidin and making iron available in CKD patients Stage 5 undergoing dialysis (CKD-5D) [15]. However, a mechanistic explanation for this beneficial effect still needs to be provided. Another long-acting recombinant ESA is methoxy-polyethylene glycol-epoetin beta (methoxy-PEG-epoetin beta, Mircera®; F. Hoffmann-LaRoche and Chugai) [16]. The plasma half-life of methoxy-PEG-epoetin beta is ~120–130 h. Methoxy-PEG-epoetin beta has proved to maintain haemoglobin (Hb) levels within the target range (100–120 g/L) in patients with CKD-5D [17]. While—biophysically—1 μg of darbepoetin alfa or methoxy-PEG-epoetin beta peptide corresponds to 200 international units (IU) rhEpo peptide, the long-acting products may enable it to reduce the doses below the predicted 1 : 200 ratio [18].

The understanding of the sites and mechanisms of the metabolism of Epo and its analogues is still incomplete [1]. Two metabolic pathways have been suggested: (i) Epo-R-mediated endocytosis by erythrocytic progenitors and (ii) Epo-R independent degradation. The prolonged action of the biobetters is partly due to a low Epo-R-binding affinity of the agents. It is important to clarify that the concentration of long-acting ESAs is proportionally higher in circulation compared with that of epoetins at appropriate dosing (Figure 2).

HIF STABILIZERS

Distinct heterodimeric hypoxia-inducible transcription factors, the HIFs (primarily HIF-2) activate the *EPO* enhancer, thereby increasing Epo production at renal and extrarenal sites

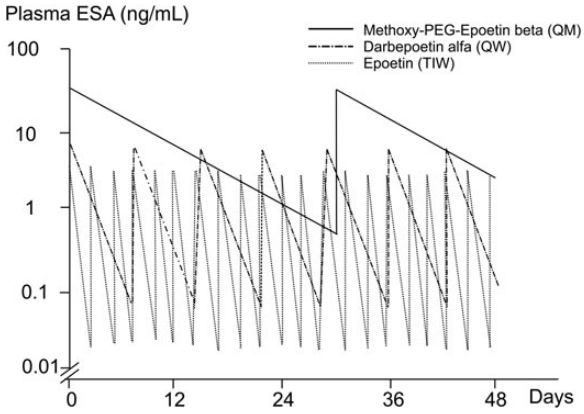

FIGURE 2: Estimates of the plasma concentrations of regular and long-acting ESAs. Calculations have been based on i.v. administrations of equal peptide amounts of regular rhEpo (2000 IU epoetin three times a week), darbepoetin alfa (30 μg once a week) and methoxy-PEG-epoetin beta (120 μg once a month), 70 kg body weight, and ESA half-lifes of 8, 25 and 125 h, respectively. Specific activity of rhEpo corresponds to 200 IU/μg peptide.

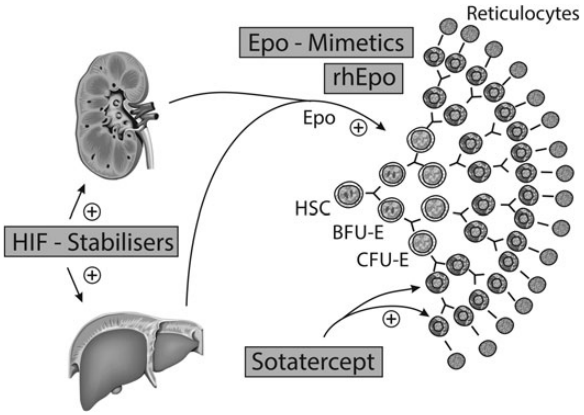

FIGURE 3: Scheme of the regulation of erythropoiesis and possible sites of pharmacological interventions. Endogenous or recombinant Epo is a survival, proliferation and differentiation factor for the erythrocytic progenitors. HIF, hypoxia-inducible factor; rhEpo, recombinant human Epo; HSC, haematopoietic stem cell; BFU-E, burst-forming unit-erythroid; CFU-E, colony-forming unit-erythroid.

[19]. The expression of *EPO* is lowered in normoxia, because specific dioxygenases promote hydroxylation of the α-subunits of the HIFs in the presence of O_2. Prolyl hydroxylated HIF-α undergoes immediate proteasomal degradation, as this is recognized by the von Hippel-Lindau tumour suppressor protein in association with an E3 ubiquitin ligase. Human tissues express three major HIF-α prolyl hydroxylases (PHDs). The HIF-α PHDs are the primary O_2 sensors controlling Epo production. In addition, the so-called factor inhibiting HIF (FIH) catalyses HIF-α asparaginyl hydroxylation. *In vitro* measurements have shown that the Michaelis constants of the enzyme–substrate complexes of the three PHDs for O_2 are appropriately high, while FIH works with lower pO_2 values [20].

The HIF-α hydroxylases require α-ketoglutarate for their catalytic action [21]. Hence, α-ketoglutarate competitors ('HIF stabilizers') prevent HIF-α elimination and stimulate *EPO* expression [19, 21, 22]. The HIF-α hydroxylase inhibitor FG-2216 (FibroGen, Inc./Astellas) proved to increase plasma Epo levels in a clinical phase I trial [23]. Interestingly, Epo levels also increased in anephric patients treated with FG-2216 [23], indicating that *EPO* expression was induced at extrarenal sites, e.g. the liver (Figure 3). The follower drug FG-4592/ASP1517 is in clinical trials in the USA, Europe and Asia. On oral application (0.7–2.0 mg/kg two or three times a week) the drug produced a dose-dependent increase in Hb levels in patients with CKD (stages 3–4) (http://www.fibrogen com/anemia 2011). FG-4592/ASP1517 has entered a phase II trial in patients with CKD-5D in Japan, and it is in clinical phase III development to support approval in the EU and the USA.

GSK1278863 (GlaxoSmithKline) is an alternative HIF stabilizer, which was successfully tested with escalating doses (up to 300 mg) in a clinical Phase I trial on healthy subjects. A phase IIa trial is underway to evaluate the safety, pharmacokinetics and efficacy of repeat doses of GSK1278863 in anaemic patients with CKD (both dialysis and pre-dialysis). Furthermore, AKB-6548 (Akebia Therapeutics), another HIF stabilizer, was reported to produce increases in plasma Epo levels in healthy volunteers without causing SAEs. Subsequently, a phase IIb randomized, double-blind, placebo-controlled study has been initiated to assess the pharmacodynamic response, safety and tolerability of AKB-6548 in pre-dialysis patients with anaemia secondary to CKD (NCT01906489).

Advantages of the HIF stabilizers—compared with recombinant proteins—include the oral route of administration and their simple chemical structure. Also, HIF stabilizers have been reported to reduce hepcidin levels [24]. In this author's mind, however, the safety of the HIF-α hydroxylase inhibitors should be investigated very carefully, before they qualify for the clinical routine. The HIFs can activate >300 genes apart from *EPO*, involving the danger of SAEs. The primary fear is promotion of tumour growth [19].

EMPs

Epo mimetic peptides (EMPs) are synthetic cyclic peptides of ~20 amino acids that show no sequence homology to Epo but signal through the Epo-R. The clinically most advanced product was peginesatide (Omontys®, originally named Hematide™; Affymax/Takeda), a pegylated homodimer of two EMPs (each ~2 kDa, total mass 45 kDa). In the first clinical report, the occurrence of neutralizing anti-peginesatide Abs was described in 1 out of 14 CKD patients who were treated with peginesatide for 28 months, as they suffered from anti-Epo Abs-induced PRCA [25]. Peginesatide proved non-inferior to darbepoetin alfa in correcting Hb levels in CKD patients not yet on dialysis (studies PEARL 1 and 2); however, cardiovascular events and mortality were increased in peginesatide-treated patients [26]. Two maintenance studies (EMERALD 1 and 2) in patients with CKD-5D found peginesatide as effective as epoetin alfa in maintaining Hb levels [27]. There was no statistical difference in SAEs in the treatment groups [27].

Owing to the prolonged action of the drug (mean half-life 48 h on i.v. administration in dialysis patients) treatment with Omontys® once monthly was sufficient to maintain Hb levels. Omontys® was approved in the USA for s.c. or i.v. treatment (0.03–0.1 mg/kg b.w., once monthly) of anaemic adult patients with CKD-5 in 2012. Just 1 year later, the drug was recalled—voluntarily by Affymax/Takeda—in view of acute hypersensitivity reactions in patients receiving Omontys® (www.fda.gov/Safety/Recalls/default.htm). Approximately 0.02% of the patients died following the first dose of i.v. administration of the drug.

In alternative approaches, EMPs have been constructed onto human IgG-based scaffolds by recombinant DNA technology. The seminal compound, CNTO 528 (Centocor), with a very long half-life (4–7 days), increased Hb levels on i.v. administration (0.03–0.9 mg/kg b.w.) in a phase I study in healthy men [28]. The follow-on product CNTO 530, a dimeric EMP fused to a human IgG4 Fc scaffold, was shown to expand the pool of erythrocytic progenitors *in vitro* and *in vivo* [29]. However, the immunogenic harmlessness of these compounds has not been described sufficiently.

ACTIVIN TRAPS

Activins are dimers of inhibin β-type chains, with activins A (β_A/β_A), AB (β_A/β_B) and B (β_B/β_B) being most common. Activins belong to the transforming growth factor-β (TGF-β) superfamily and signal through type I (ActRI) and type II (ActRIIA or ActRIIB) serine/threonine kinase receptors [30]. Activin binding to ActRII causes activation of ActRI, which phosphorylates cytoplasmic small mothers against decapentaplegic proteins (SMADs). In particular, SMAD4 affects the expression of a large variety of genes [31]. When Yamakawa *et al.* [32] produced transgenic chimeric mice, in which the soluble IgG1-Fc fusion protein of three bone morphogenic protein (BMP) type II receptors (ActRIIA, ActRIIB, BMPRII) was highly expressed, some unexpected phenotypes were identified, including increased extramedullary haematopoiesis in the spleen and elevated RBCs.

Sotatercept (ACE-011; Acceleron/Celgene) is a chimeric protein consisting of the extracellular part of ActRIIA and the Fc domain of human IgG1. Sotatercept traps circulating activin and related proteins, such as BMP 10 and BMP 11 [33], and it prevents their action on the endogenous, membranous, ActRIIA [34]. In a double-blind, single-dose escalation phase I study, 48 women were randomized to receive either a single-dose of sotatercept or placebo. Treatment with sotatercept was found to reverse bone loss and to reduce the degree of osteoporosis [35]. A single i.v. injection of the highest dose of sotatercept (3 mg/kg b.w.) resulted in an increase in Hb levels, RBC numbers and haematocrit [35]. Adverse events were reportedly mild and no anti-drug Abs were detected. The pharmacokinetics, safety, efficacy, tolerability and pharmacodynamics of sotatercept (starting dose of 0.1 mg/kg b.w., s.c.) are currently being tested in a Phase IIa study in patients with CKD-5D (NCT01146574). Provided sotatercept can stimulate erythropoiesis in patients with renal anaemia, less recombinant ESA may be necessary for their care (Figure 3). However, the mechanisms underlying the erythropoietic action of sotatercept still need to be identified. There are a few more Phase II trials examining the effects of sotatercept in anaemia, including chemotherapy-associated anaemia due to multiple myeloma (NCT00747123), solid tumours (NCT01190644), Diamond-Blackfan anaemia (NCT01464164), transfusion-dependent β-thalassaemia (NCT01571635), and myelofibrosis [36]. There are also clinical trials being performed with ACE-536 (Acceleron/Celgene), another investigational ActRII fusion protein that acts as a ligand trap for members in the TGF-β superfamily.

The mechanisms underlying the alleged beneficial effects of sotatercept and its analogue on erythropoiesis are still poorly understood. Remember that activin A is identical with the so-called 'erythroid differentiation factor' (EDF) [37], known to induce the *in vitro* differentiation of immature erythrocytic progenitors into mature Hb-synthesising cells [38]. Activin A was earlier reported to directly promote Hb synthesis and to indirectly (via accessory marrow cells) stimulate erythroid cell proliferation and DNA synthesis [39]. EDF was also shown to facilitate maintenance of burst-forming units-erythroid (BFU-Es) through a humoral activity secreted by bone marrow stromal cells [40]. Other investigators demonstrated erythroid-stage specific actions of activin A/EDF and an increase in mature BFU-Es and CFU-Es in primary cultures of $CD34^+$ cells [41, 42]. Recombinant human EDF (rhEDF) was found to increase the sensitivity of BFU-Es cultured from bone marrow of CKD patients towards rhEpo [43]. This led to the proposal that, in patients with renal anaemia, concomitant administration of EDF might increase the therapeutic efficacy of rhEpo therapy by enhancing the sensitivity of progenitor cells to rhEpo, thereby decreasing the therapeutic dose of rhEpo [43]. Finally, rhEDF administered to rodents was reported to produce a dose-dependent rise both in myeloid BFU-Es and CFU-Es [44].

In an attempt to solve this apparent contradiction, Ianca-Rubin *et al.* [45] have recently re-investigated the role of the ActR system in erythropoiesis. While sotatercept did not directly affect erythroid differentiation of human $CD34^+$ cells *in vitro*, the stimulatory activity of sotatercept was related to cellular or soluble factors present within the bone marrow microenvironment [45]. E.g. sotatercept increased the expression of angiotensin II, which can stimulate erythropoiesis directly and indirectly via Epo production [45]. Further, sotatercept reduced the expression of vascular endothelial growth factor considered an inhibitor of erythropoiesis [45].

There is another interesting aspect. Sotatercept can inhibit hepcidin transcription in the liver [46]. Excess hepcidin is the root cause of the hypoferraemia and iron-restricted erythropoiesis in CKD [47, 48]. The hepcidin promoter contains BMP-responsive SMAD-binding elements [49], apart from interleukin 6-responsive STAT3-binding elements. Activin B has a crucial role in the induction of hepcidin by inflammation [24], and it is therefore a specific target for the treatment of anaemia of inflammation [50]. Bruno *et al.* [51] have reported earlier that inhibition of SMAD5, which mediates BMPs signalling through ActRIIA, reversed TGF-β-mediated inhibition of erythrocytic progenitors.

CONCLUSIONS

CKD is a global healthcare problem, its incidence increases and drives health service costs. RhEpo therapy can prevent RBC transfusion-dependent anaemia in practically all CKD patients, provided care is taken for sufficient iron supplementation. Less expensive biosimilar epoetins have entered the market and compete with the innovator epoetins and their long-acting analogues. Darbepoetin alfa and methoxy-PEG-epoetin beta offer the advantage of less frequent dosing schedules, possibly the dose requirements may also be reduced.

Clinicians need to be familiar with the various types of recombinant ESAs and to understand the similarities and differences of the products. Indeed, a change from one licensed epoetin to another is allowed, even in strictly controlled regions, however, only with the consent of a physician. Some of the products are co-marketed with different trade names, these are identical and among themselves substitutable by pharmacists. While the biosimilars that have been approved in developed countries are of high pharmaceutical quality, this may not be the case with all products in developing countries. In addition, problems still exist with respect to the naming of the epoetins, since most products have been named 'epoetin alfa' despite differences in structure and formulation compared with the originator.

Practical disadvantages of all recombinant ESAs relate to the fact that they require cold storage and parenteral administration. In contrast, HIF stabilizers such as α-ketoglutarate competitors are stable, small synthetic molecules that can be administered orally. In patients with renal failure, HIF stabilizers can induce Epo production at extrarenal sites such as the liver. Various HIF stabilizers are in the clinical test phase. However, HIF stabilizers activate numerous other genes apart from *EPO*; the most critical danger is the support of tumour growth.

EMPs bind to the Epo-R and induce the same intracellular signals like Epo. One EMP prototype was peginesatide, a pegylated EMP dimer. However, after 1 year of widespread use in the USA, peginesatide (Omontys®) was recalled in 2013 because of its intolerance. The hypersensitivity reactions caused by peginesatide were not foreseeable. Two other EMPs are still in the clinical test phase. It is to be hoped that the patients' safety is adequately protected in the lucrative race to get products on the market. As far as possible, physicians should remain free of economic burdens and be able to stick to the Hippocratic Oath notion: 'to abstain from doing harm'.

In particular, stringent safeguards should be required for testing new biological drugs like the ActRIIA fusion protein sotatercept [36], whose effects on erythropoietic tissues are still poorly understood. The reported ability of activin to favour *in vitro* erythroid differentiation [37] is difficult to reconcile with the clinical observations that an activin antagonist such as sotatercept stimulates erythropoiesis.

In conclusion, new developments may become available which supplement and optimize anaemia management. At present, however, the alternative therapies are far from entering the clinical routine. Recombinant ESAs, including the biosimilar epoetins and the long-acting analogues will remain the mainstay of the anti-anaemia therapy in the coming years.

CONFLICT OF INTEREST STATEMENT

The author has had a compensated consultant/advisory role and received honoraria and research funding from pharmaceutical companies producing and/or marketing ESAs. The author declares that the results presented in this paper have not been published previously in whole or part, except in abstract format.

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