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Differentiating Factors Between Erythropoiesis-Stimulating Agents

A Guide to Selection for Anaemia of Chronic Kidney Disease

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Contents

Abstract

Endogenous erythropoietin (EPO) consists of a central polypeptide core covered by post-translationally linked carbohydrates. Three of the four currently available erythropoiesis stimulating agents (ESA) – epoetin-α, epoetin-β and epoetin-ω – are composed of an identical amino acid sequence, but glycosylation varies as a result of type- and host cell-specific differences in the production process.

Epoetin-α and epoetin-β resemble each other with respect to molecular characteristics and pharmacokinetic data, although epoetin-β has a higher molecular weight, a lower number of sialylated glycan residues and possibly slight pharmacokinetic advantages such as a longer terminal elimination half-life. A serious adverse effect of long-term administration of ESA is pure red cell aplasia. This effect has been observed predominantly with subcutaneous use of epoetin-α produced outside the US after albumin was removed from the formulation. In comparison with the intravenous route, subcutaneous administration of epoetin has been reported to have a dose-sparing effect in some studies. Epoetin-β has been the subject of studies aimed at proving efficacy with a reduced administration frequency but results are not unequivocal.

Epoetin-ω is produced in a different host cell than all other erythropoietic agents, hence glycosylation and pharmacokinetics are different. Small-scale clinical studies found epoetin-ω to be slightly more potent than epoetin-α.

Epoetin-δ is a recently approved agent produced by human cells that are genetically engineered to transcribe and translate the EPO gene under the control of a newly introduced regulatory DNA sequence. However, epoetin-δ is not yet on the market and few data are available.

The erythropoietin analogue darbepoetin-α carries two additional glycosylation sites that permit a higher degree of glycosylation. Consequently, in comparison with the other epoetins, darbepoetin-α has a longer serum half-life and a higher relative potency, which further increases with extension of the administration interval. Dosage requirements of darbepoetin-α do not appear to differ between the intravenous and subcutaneous routes of administration. The less frequent administration of darbepoetin-α in comparison to the other epoetins may reduce drug costs in the long term, but the variability in dosage or dosage frequency required within a single patient is high.

Further studies should be aimed at defining predictors of the individual demand for erythropoietic agents, thereby allowing nephrologists to prescribe a cost-effective, individualised regimen.

Red cell production in the bone marrow is dependent upon the coordinated action of several different cytokines and hormones. In concert with others, erythropoietin (EPO) determines the proliferation of erythroid progenitor cells, in particular burst-forming unit erythroid (BFU-E) cells, colony-forming unit erythroid (CFU-E) cells and normoblasts.[1,2] EPO binds to the extracellular domain of the EPO receptor and adequate signalling occurs after dimerisation of two monomers. Erythroid cells at the CFU-E and pronormoblastic stage have been reported to carry the highest numbers of EPO receptors per cell, while reticulocytes and mature erythrocytes appear to be free of EPO receptors.[3-5] After binding to its receptor, EPO opposes programmed cell death and, as such, decreases the number of apoptotic erythroid precursors.

Endogenous EPO is produced predominantly in renal peritubular, fibroblast-like cells.[6] In patients with failing kidneys, EPO release is inadequate in relation to oxygen demands. Potential causes include: destruction of the normal renal microvasculature interfering with adequate oxygen sensing; elevation of the peritubular oxygen pressure beyond levels required to stimulate adequate EPO release;[7] transformation of EPO-producing renal peritubular, fibroblast-like cells into matrix-producing myofibroblasts; disruption of the normal paracrine signals derived from adjacent interstitial and epithelial cells; accumulation of pro-inflammatory cytokines inhibiting EPO production;[8] autonomic sympathetic dysfunction;[9] and inadequate compensation by the liver.[10] In large population cohorts it has been shown that haemoglobin levels fall significantly when the glomerular filtration rate falls below 70 mL/min in men or below 50 mL/min in women.[11] Diminished erythrocyte survival as a result of uraemia and chronic blood loss via the extracorporal circuit or by occult gastrointestinal bleeding contribute further to the genesis of anaemia of chronic kidney disease.

Anaemia constitutes an independent risk factor for the development of left ventricular hypertrophy, heart failure and cardiac mortality.[12,13] Correction of anaemia, therefore, is mandatory. Cardiac output, left ventricular volume and wall thickness have been shown to decrease with partial correction of anaemia by the administration of erythropoiesis-stimulating agents (ESAs).[14] Furthermore, beneficial effects of anaemia correction include improvement of quality of life, nutritional status, exercise tolerance, sexual function and glucose metabolism as well as clotting dysfunctions.[8]

At present, various types of ESAs are available and more will be marketed in the future. The first part of this review deals with differences in molecu-

lar composition of the various ESAs. In the second part, clinical data are discussed with respect to guiding selection for the treatment of anaemia of chronic kidney disease. In this review, the term ESAs denotes all erythropoietic agents, and epoetin stands for epoetin-α, -β, -δ (delta) or -ω (omega).

1. Endogenous Erythropoietin (EPO)

In endogenous EPO, the polypeptide core of 165 amino acids bears four glycosylation sites that carry three N-linked (at asparagine 24, 38 and 83) and one O-linked (at serine 126) oligosaccharide chains,[15] amounting to approximately 40% of the molecular mass. Structural determination studies revealed that the glycosylation sites are localised at one end of the molecule, distant to the receptor binding site.[16,17] Accordingly, a reduction of N-glycosylation sites by site-directed mutagenesis does not decrease binding affinity to the EPO receptor.[18] Glycosylation occurs post-translationally, and structural differences of the four glycan residues result in numerous diverse isoforms of the molecule.[19] In particular, the three N-linked carbohydrate chains may contain 2–4 oligosaccharide branches, each terminated with a negatively charged sialic acid. The O-linked sugar chain carries up to two sialic acid residues. The total number of sialic acid residues determines the net negative charge of the molecule, and an isoform of EPO is defined as the subset of molecules with the same charge due to the same number of sialic acid residues.[20]

The biological activity and fate of EPO are largely determined by the N-linked carbohydrate residues. The O-linked oligosaccharide does not appear to affect *in vitro* and *in vivo* activity,[21,22] similar to findings on recombinant human granulocyte colony-stimulating factor.[23] In mice, EPO isoforms with a higher negative charge due to higher sialic acid residue content were shown to exhibit a greater *in vivo* efficacy, a longer serum half-life and a slower serum clearance in comparison to the lesser charged isoforms.[20]

It is the change in serum clearance that appears to predominantly affect *in vivo* activity, although receptor-binding studies revealed a decreasing affinity with increasing sialic acid content.[20] Degradation of circulating EPO theoretically occurs via hepatic uptake, renal clearance and/or EPO-receptor mediated uptake as well as intracellular degradation.[24] Although hepatocytes bear receptors for galactose, and may thus clear desialylated glycoproteins such as asialo-EPO, experimental studies on mice and sheep found no association between the clearance of exogenous EPO and impaired liver function.[25,26] Similarly, clearance of epoetin was unaltered in patients with chronic kidney disease when compared with normal individuals.[27] Since EPO clearance from plasma follows non-linear models[28] compatible with a transient saturation of EPO receptors,[29] EPO-receptor dependent variation of plasma half-life appears feasible.[24] Interestingly, the *in vitro* receptor-binding affinity of the hyperglycosylated darbepoetin-α is 4.3-fold lower than that of epoetin, in accordance with the prolonged half-life of darbepoetin-α.[20]

2. Overview of Recombinant Erythropoiesis-Stimulating Agents

2.1 The Epoetins

Epoetins are recombinant human erythropoietins that are composed of the same amino acid sequence as endogenous EPO. However, glycosylation varies and the three currently commercially available types of epoetin (α, β and ω) contain a higher proportion of sialylated, acidic carbohydrate residues than endogenous EPO.[30] Epoetin-α (Procrit®[1], Epogen®, Eprex®) is widely available, and epoetin-β (Neorecormon®, Recormon®) is presently available in Europe and other non-US countries. Epoetin-ω (Epomax®) is the most recently launched and is available in some but not all countries at this stage. The key characteristics of these epoetins are compared in table I. As discussed later in this section, a fourth form of epoetin (epoetin-δ)

1 Use of brand names is for product identification purposes only and does not imply endorsement.

Table I. Some key parameters of erythropoiesis-stimulating agents[20,24,30-37]

	Epoetin-α	Epoetin-β	Epoetin-ω	Darbepoetin-α
Carbohydrate proportion (%)	40	40	ND	52
Number of N-linked carbohydrates	3	3	3	5
Number of sialic acid residues per molecule	≤14	≤14	ND	≤22
Proportion of tetra-sialylated carbohydrate residues (%)	19	46	21; 50[a]	ND
Proportion of isoforms with O-linked carbohydrates (%)	95	ND	60	ND
Half-life (h):				
IV route	4–11	8.8–10.4	ND	18–25.3
SC route	19–25.3	24	ND	48.8
Clearance (IV route) [mL•h^{-1}•kg^{-1}]	8.1–8.6	7.9	ND	2.0
Bioavailability (SC route) [%]	30–36	15–50	ND	37
Frequency of administration (×/week)	1–3	0.5[b]–3	1–2	0.5[b]–1
Relative potency[c]:				
thrice weekly	1	1–1.2	~1.3	3.6
once weekly	1	ND	ND	13–20
Conversion factor	1	ND	ND	200IU : 1μg (up to 433 : 1[d])

a Divergent reports.[30,33]

b 0.5×/week = once every 2 weeks.

c As assessed from animal studies.

d Depending on dose of epoetin-α (up to 33 999 U/week).

IV = intravenous; **ND** = no data; **SC** = subcutaneous; **×/week** = times per week.

is also expected to be available in Europe in the future.

Epoetin-α and -β are produced by Chinese hamster ovary cells (CHO) transfected with the authentic human EPO gene. After culturing, a stepwise producer-specific, chromatographic isolation procedure follows. Cell culture conditions and protein purification steps largely determine molecular size and charge of the glycosylated endproduct. Hence, glycosylation of the recombinant products differs from that of endogenous EPO,[30,38] and epoetin-α and -β differ by size and charge.

Epoetin-β has a higher molecular weight, contains a wider spectrum of isoforms, and has a higher proportion of more basic isoforms, consistent with a lower number of sialylated glycan residues than epoetin-α.[39] The proportion of tetra-sialylated carbohydrate residues, however, is highest in comparison with other epoetins (see table I).[30] In mice, desialylation of EPO has been reported to decrease its biological activity,[20] but the *in vivo*/*in vitro* bioactivity ratio was found to be more than 20% higher for epoetin-β than for epoetin-α.[39]

In a randomised, crossover study of 18 healthy young men, epoetin-β showed a longer terminal elimination half-life than epoetin-α after intravenous or subcutaneous administration, as well as significantly delayed absorption after subcutaneous administration that was followed by a more pronounced reticulocytosis than epoetin-α.[31] No differences in biological half-life were observed between epoetin-α and -β among patients with chronic kidney disease who were on haemodialysis or peritoneal dialysis.[32] Nevertheless, the more favourable pharmacokinetic properties of epoetin-β in comparison to epoetin-α may counterbalance the lower degree of sialylation.

Epoetin-ω is engineered in baby hamster kidney (BHK) cells.[40] In contrast to the CHO cell-derived epoetins, only 60% of epoetin-ω is O-glycosylated at the serine residue 126.[33] The major oligosaccharide structures are of the tetra-antennary type, and a higher proportion of carbohydrate residues are tetra-sialylated when compared with endogenous EPO, as has been reported for the other epoetins (see table I).[30,33] In addition, one of the N-glycosylation sites of epoetin-ω contains a phosphorylated oligoman-

nosidic side-chain.[41] The glycosylation pattern of epoetin-ω resembles that of recombinant human interleukin-2 produced in BHK cells.[42]

In 2002, European authorities approved a new type of epoetin for the treatment of anaemia associated with chronic kidney disease. Epoetin-δ, also called gene-activated™ erythropoietin or Dynepo™, is produced by human cells that are genetically engineered to transcribe and translate the EPO gene under the control of a newly introduced regulatory DNA sequence. Introduction of the new sequence was achieved by homologous recombination of non-coding DNA. The term 'gene-activation' means control of gene expression by newly introduced promoter regions to coding, native DNA sequences.[43] Expression of target molecules by human cells circumvents problems arising from species-dependent differences in protein folding or post-translational modification. More than 1400 patients have participated in phase III clinical trials of epoetin-δ conducted in the US and UK, but marketing was delayed because of litigation concerning potential patent infringements.

2.2 The EPO Analogue Darbepoetin-α

Darbepoetin-α is a hyperglycosylated EPO analogue designed for prolonged survival in the circulation and thus greater biological activity; the key characteristics of this agent are compared to those of the epoetins in table I. The amino acid sequence of darbepoetin-α differs from that of endogenous EPO at five positions, allowing attachment of two additional N-linked oligosaccharides at the asparagine residues in position 30 and 88 without destruction of the conformation.[20] Like epoetin-α and -β, darbepoetin-α is produced in CHO cells. Because of the tetra-antennary branching of the carbohydrate chains, darbepoetin-α may carry up to eight additional sialic acid residues.[20]

Consequently, the terminal half-life of intravenous darbepoetin-α was estimated to be 3-fold longer than intravenous epoetin-α (25.3 vs 8.5 hours), and the time to peak concentration after subcutaneous application was more than doubled with darbepoetin-α compared with epoetin-α (54 vs 16–24 hours), in peritoneal dialysis patients.[34] In mice, darbepoetin-α administered three times weekly intravenously, intraperitoneally or subcutaneously was found to be 3.6-fold more potent than epoetin-α.[35] The relative potency of darbepoetin-α increases with longer application intervals (see table I).

In contrast to quantifying the activity of endogenous EPO and epoetin in units, concentrations and doses of darbepoetin-α are given in μg peptide with the carbohydrate portion not taken into account. Based on the peptide mass, 200IU of epoetin-α is equivalent to 1μg of darbepoetin-α.

2.3 Continuous Erythropoiesis Receptor Activator

Continuous efforts to identify more potent ESAs led to the development and identification of continuous erythropoiesis receptor activator (CERA), a molecule that is composed of a protein core, a single methoxy-polyethylene glycol polymer and a succidinmidyl butanoic acid linker.[44] *In vitro*, CERA dissociates faster from the soluble erythropoietin receptor than epoetin-β and cellular proliferation is stimulated to a lower degree by CERA than by epoetin-β. However, in normocythaemic mice, CERA induces a greater increase of reticulocyte counts than identical protein amounts of epoetin-β. Therefore, CERA is believed to exert a stronger erythropoietic stimulus on erythroid progenitor cells than epoetin-β. It is speculated that the binding of CERA to the erythropoietin receptor is too brief for internalisation, and that the presumedly greater stimulating action of CERA on the erythropoietin receptor results from repeated cycles of receptor binding, stimulation and dissociation, which is supported by an extended serum half-life of CERA even in comparison with epoetin-β.[44]

Preclinical studies in mice used reticulocyte and erythrocyte counts to assess erythropoietic activity and found CERA to be a more potent stimulator of erythropoiesis than epoetin (type not specified; absolute amounts compared). Stimulation of erythropoiesis was dose-dependent, and once weekly and once every other week administrations were equally

effective. Pharmacokinetic studies found the systemic clearance of CERA to be much lower compared with that of epoetin, resulting in a 2- and 7-fold increase of serum half-life of CERA in rats and dogs, respectively.[45]

A single phase I trial ascertained the pharmacodynamic efficacy and tolerability of CERA in single and multiple ascending dose protocols.[46] Both intravenous and subcutaneous administrations resulted in dose-dependent increments of reticulocyte counts. Phase II studies exploring dose administration flexibility of CERA in patients with chronic kidney disease are underway.

3. Clinical Use of Epoetin-α versus Epoetin-β

To date, there are no valid reports documenting any significant differences between epoetin-α and -β with regards to the correction of renal anaemia. Current guidelines[47,48] do not differentiate between these agents. The dosage, clinical efficacy and effects on quality of life appear to be comparable.

Tolerability of the subcutaneous route of administration may depend on the conditioning of the EPO-preparations. Phosphate-buffered epoetin-α caused less pain at the injection site than citrate-buffered epoetin-α,[49,50] and epoetin-β was even less painful being comparable to normal saline.[50] Furthermore, the multi-dose formulation of epoetin-α, containing benzyl alcohol, caused less discomfort locally than single-dose formulations.[51] The subcutaneous route may not be applicable for all forms of epoetin. Pure red cell aplasia, associated with neutralising antibodies to endogenous EPO, has been attributed to long-term use of erythropoietic agents. The vast majority of cases were observed after subcutaneous administration of Eprex® (epoetin-α) produced outside the US after removal of human serum albumin from the formulation in 1998.[52] Consequently, approval of subcutaneous administration of epoetin-α was withdrawn in Europe. Of primary importance in the generation of antibodies to the EPO molecule may be the cocktail of added stabilisers (human serum albumin, glycine, urea, polysorbate 80 or 20, respectively).[53]

The efficiency of epoetin may largely depend upon the route of administration. All major guidelines recommend subcutaneous administration, although bioavailability is only about one-third of that estimated for intravenous administration (see table I). The weekly dosage of epoetin required for therapeutic effect has been reported to be 15–50% lower with subcutaneous compared with intravenous administration.[47] The potential dose-sparing effect has been attributed to the extended half-life after subcutaneous administration (see table I), resulting in a sustained stimulation of erythroid progenitor cells. Furthermore, a sudden drop in circulating erythropoietin levels after intravenous administration may cause lysis of young erythrocytes. A recent meta-analysis of 27 prospective clinical trials with 916 patients found an average reduction of nearly 50 IU/kg/week with subcutaneous versus intravenous administration of epoetin. The lower subcutaneous dosage is compatible with an average drug cost saving of approximately 30%.[54] In contrast, results from the European Survey on Anaemia Management (ESAM) study showed a nonsignificant difference of 9 IU/kg/week in subcutaneous and intravenous dosages, but these data were retrospective and the target haemoglobin levels varied widely.[55] The issue is not clear cut, and others have reported that the dosage required and effects achieved are not significantly affected by the route of administration.[56] Furthermore, a significant proportion of patients may need more epoetin after switching to the subcutaneous route.[57]

To date there is no valid evidence to support the efficacy of once weekly intravenous epoetin, however, once weekly subcutaneous administration may be as effective as more frequent subcutaneous administration regimens. A meta-analysis looking at the effect of different frequency regimens of epoetin administration in dialysis patients showed no significant differences in the correction of anaemia, quality of life, adverse events and efficacy between once weekly versus more than once weekly subcutaneous administration.[58] Validity of this analysis, however, is limited by the small number of studies/participants included, and the variability in study

duration and frequency regimens.[58] In a randomised, multicentre therapeutic-equivalence study of 134 stable haemodialysis patients, once weekly subcutaneous epoetin-β was found to be equivalent to three times weekly treatment with respect to stable haematocrit levels, required dose and tolerability.[59] However, there was a tendency for lower haematocrit levels and higher required epoetin-β doses in the patients receiving subcutaneous epoetin-β once weekly as compared with those receiving epoetin-β three times per week. This tendency, although within the pre-specified equivalence range, was found to be more pronounced with per-protocol than with intention-to-treat analysis. These results suggest that there may be a true impact of less frequent epoetin-β administration on the primary endpoints of haematocrit and required epoetin-β dose. In healthy volunteers, absorption of epoetin-α from the subcutaneous site is independent of the dose, while clearance decreases in a non-linear fashion with increasing dose.[60] The assumed equivalency of once- versus thrice-weekly administered subcutaneous doses of epoetin might, therefore, result from a reduced clearance with higher doses. However, the study duration (24 weeks) may have been too short, and the 'haematocrit' endpoint may be less accurate than haemoglobin concentrations.[61]

In end-stage renal failure, an individual critical plasma EPO threshold has been postulated for effective erythropoiesis[62] and the administration interval should be determined by when trough values fall below this threshold. During once-weekly administration of subcutaneous epoetin-β, EPO plasma levels dropped below this threshold by the fourth day.[63] In healthy adults, an equivalent pharmacodynamic response was observed with once weekly subcutaneous administration of epoetin-α at a dose that was 30% higher than the total dose given by thrice-weekly administration.[64] Epoetin-α administered subcutaneously to patients with chronic kidney disease in 3-week intervals was clearly insufficient to maintain stable haemoglobin levels.[65] Only recently, a 2-week interval regimen was approved in the European Union for subcutaneous administration of epoetin-β in dialysis patients.[66]

Clearly, reduced epoetin administration frequency allows flexibility of administration, individualisation of administration regimens and facilitation of self-administration.[67] Dose administration frequency may be inversely linked to the absolute number of sialic acid residues or the proportion of tetra-sialylated carbohydrate branches (see table I). Further clinical trials are necessary to evaluate the efficacy of prolonged administration intervals.

4. Clinical Use of Epoetin-ω

Epoetin-ω has been subject of only a few clinical studies. Two uncontrolled studies demonstrated an effective increase in haemoglobin concentration in end-stage renal disease patients both on short-[68] and long-term[69] haemodialysis. Results from a nonrandomised, prospective crossover trial of 38 patients on stable maintenance haemodialysis found that the mean weekly dosage of subcutaneous epoetin-ω needed to maintain target haemoglobin levels is about 20% less than that of epoetin-α.[70] According to the supplier, initial dosages of intravenous or subcutaneous epoetin-ω range from 25 to 50 IU/kg bodyweight, twice weekly. Weekly average maintenance dosages vary between 20 and 80 IU/kg bodyweight. Once-weekly administration of epoetin-ω has been reported to be effective in dialysis patients,[71] but it is not clear whether the relative potency increases with prolonged administration intervals as has been observed for darbepoetin-α (see section 2.2).

5. Clinical Use of Darbepoetin-α versus Epoetin-α

To date, several clinical studies on the efficacy and safety of darbepoetin-α have been conducted. Trials in chronic kidney disease, haemodialysis or peritoneal dialysis patients found an initial once weekly intravenousor subcutaneous dosage of 0.45–0.75 μg/kg bodyweight to be effective and have a good safety profile.[72,73] No significant differences in weekly dosage requirements have been observed between the intravenous and subcutaneous routes of administration.[73,74]

A randomised, double-blind efficacy study comparing thrice weekly intravenous epoetin (type not specified) with once weekly darbepoetin-α determined that the regimens were equipotent.[75] One hundred and sixty-nine of 507 dialysis patients were switched to darbepoetin-α, dose conversion was based on the peptide mass (200 IU epoetin = 1μg darbepoetin-α). More than two-thirds of all patients required a change of dosage to maintain target haemoglobin levels during the titration period, and nearly half of the patients required a change of dosage during the evaluation period.[75]

Another study reported intravenous darbepoetin-α, given once per week or once every other week, to be more potent than intravenous epoetin (type not specified) administered two to three times per week or once weekly, respectively.[76] Again, dosages were initially converted according to peptide mass (200IU : 1μg). After 24 weeks, 36% of dialysis patients required a dosage reduction and the mean intravenous dose required was 18% lower with darbepoetin-α than with epoetin.[76] Further analysis revealed that the relationship between the maintenance dosage of darbepoetin-α and epoetin is non-linear. Epoetin-α was found to be increasingly inefficient at higher dosages in comparison to darbepoetin-α.[36,77]

Thus, consistent with the initial clinical data,[34] darbepoetin-α seems to be more potent on a peptide mass basis than epoetin despite the reduced frequency of administration. The clearance of higher once weekly dosages of darbepoetin-α may decrease disproportionately in comparison to thrice weekly epoetin.[36,60] Mean observed dosage ratios ranged from 300IU : 1μg (at 2500–4999 IU epoetin/week) to 433 : 1 (at 18 000–33 999 IU epoetin/week) [type of epoetin not specified].[36] Variation of the conversion ratio is high, as individual dosage requirements of epoetin may vary widely.[78]

Further studies to evaluate extended administration regimens of darbepoetin-α are under way. In one study, 19 of 22 dialysis patients maintained their target haemoglobin levels for up to 20 weeks with darbepoetin-α administered only once every 4 weeks.[79]

6. Conclusion

Selection criteria for ESAs should be based on both pharmacokinetic and pharmacodynamic data, as well as on the ensuing potential for less frequent administration.

For haemodialysis patients, the intravenous administration of all ESAs may be more applicable because the existing venous access can be utilised. If given intravenously, epoetin-α or -β should be administered three times per week, darbepoetin-α once per week.

Subcutaneous administration of epoetin-α and -β has been reported to have a dose-reducing effect in comparison to the intravenous route in some studies. Furthermore, dose administration frequency may be reduced to twice or once weekly, or possibly even longer if new data for epoetin-β and darbepoetin-α are further substantiated. However, the data do not unequivocally support longer interval dosage regimens for all patients and individualising of dosage regimens remains important. Subcutaneous administration may be more convenient for peritoneal dialysis or end-stage renal failure patients who can self-administer the subcutaneous formulation at home. However, the subcutaneous administration of epoetin-α (Eprex®, Erypo®) is not permitted in certain countries because of the risk of developing pure red cell aplasia.

Administration requirements for darbepoetin-α do not differ between routes of administration. Compared with epoetin, darbepoetin-α may safely be administered less frequently. The advantage of darbepoetin-α over epoetin in terms of lower dosage requirements may be greater in patients who require dosages in the higher ranges, as evidenced by reported higher conversion ratios for epoetin versus darbepoetin-α with higher dosages.

Epoetin-ω, epoetin-δ and CERA constitute the most recently developed ESAs. All three may prove efficacious in clinical trials but results of large-scale clinical studies are pending.

Relative potencies differ between the different ESAs but, to date, there is no evidence that one drug is more effective in stimulating erythropoiesis than another. Less frequent administration may spare

clinical resources and, more importantly, may promote self-administration, tolerability and compliance of patients. Extension of the administration interval may be of benefit for patients with chronic kidney disease, patients on peritoneal dialysis or patients who have undergone kidney transplantation. Less frequent administration may prove to be more efficient in some patients; however, individuals with a high demand for epoetin or darbepoetin-α may benefit from more frequent administration because of a higher individual threshold for effective erythropoiesis.

Further studies should be aimed at defining predictors of the individual demand for erythropoietic agents, thereby allowing nephrologists to prescribe a cost-effective, individualised regimen.

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