Between subjects variability in haemoglobin and dose are not associated with the erythropoiesis-stimulating agent used to treat anaemia in dialysis: a meta-analysis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Between patients variability in haemoglobin (Hb) levels in end-stage renal disease patients enrolled in clinical trials evaluating different erythropoiesis-stimulating agents (ESAs) is around 1.0 g dL⁻¹ (standard deviation). The consistency of Hb variability estimates in clinical trials might indicate that it is independent across ESAs, despite their different pharmacokinetic and pharmacodynamic characteristics. However, some authors have hypothesized that longer acting ESAs might have the potential to reduce Hb variability.

WHAT THIS STUDY ADDS

- In the absence of head-to-head comparison in dialysis patients, we performed an indirect comparison through a meta-analysis of randomized clinical trials to explore the effect of the ESAs and their administration patterns on the mean and between-subject variability of both Hb and ESA dose. We found that, at the population level, between subject variability in Hb and ESA dose administered to dialysis patients are not associated with the type of ESA, nor with the dosing interval or route of administration, except for higher dose requirements in PEG-EPO monthly administration relative to every 2 weeks or rHuEPO i.v. relative to s.c. dosing. These findings suggest that between subject variability of both Hb and titrated ESA dose levels are intrinsic factors associated with the disease and its comorbidities.

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Keywords

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AIMS

We aimed to compare mean and between subject variability in haemoglobin (Hb) and erythropoiesis-stimulating agents (ESA) dose across the ESA compounds used to treat anaemia in dialysis patients.

METHODS

We performed a meta-analysis of randomized trials evaluating ESA in adult patients with chronic kidney disease on dialysis (target Hb 9–13.5 g dL⁻¹), and compared mean Hb and its standard deviation (SD), and ESA dose and its coefficient of variation (CV) between the different agents [rHuEPO alfa or beta, darbepoetin alfa, pegylated-epoetin beta (PEG-EPO) or other epoetins]. The effect of route and frequency of administration, frequency of dose adjustments, study blinding and type, baseline value, Hb target and sampling frequency were also assessed.

RESULTS

Among 4983 patients from 16 studies, pooled Hb mean and SD during the evaluation phase were 11.5 g dL⁻¹ (95% CI 11.3, 11.7) and 0.99 g dL⁻¹ (0.88, 1.09), respectively. The Hb mean and SD were not significantly influenced by the covariates tested. Only Hb SD was significantly lower in maintenance studies relative to correction studies. No differences in mean ESA dose and CV were found across the covariates, except that PEG-EPO monthly dose was 42% higher than the every 2 weeks dose and the rHuEPO i.v. dose was 32% higher than the s.c. dose.

CONCLUSIONS

Between subject variability in haemoglobin and ESA dose in dialysis patients is not associated with the type of ESA, nor with the dosing interval or route of administration, except for higher dose requirements in PEG-EPO monthly administration relative to every 2 weeks or rHuEPO i.v. relative to s.c.

Introduction

The concept of haemoglobin (Hb) variability in dialysis patients has recently received considerable attention in the literature [1–4]. This variability may be assessed over time within the same subject or between individuals in a group of patients at certain time points. Among haemodialysis patients treated with erythropoiesis-stimulating agents (ESAs), there is considerable within patient variability in Hb [5], which has been associated with increased mortality risk in large observational studies [1]. However, recent data demonstrate that this relationship is largely confounded by comorbidities or intercurrent events [6–8], such as episodes of infection or inflammation, hospitalization, blood loss, fluid gain during the interdialytic period, laboratory measurement errors, intermittent iron therapy and a narrow Hb target range, among others [3, 4]. The ESA dosing protocol may also influence Hb levels over time within an individual and might contribute to increase Hb variability in patients with chronic kidney disease (CKD) [9]. However, this effect appears minimal compared with the effect of the previously mentioned factors [5].

With respect to between patient variability in the general haemodialysis population, the standard deviation (SD) around the mean Hb has been reported to vary from 1.3 to 1.5 g dl⁻¹. These estimates are higher than 1.0 g dl⁻¹, the Hb SD typically observed in end-stage renal disease (ESRD) patients enrolled in clinical trials evaluating different ESAs. The consistency of Hb variability estimates in clinical trials might indicate that it is independent across ESAs, despite their different pharmacokinetic and pharmacodynamic (PKPD) characteristics. However, some authors have hypothesized that longer acting ESAs might have the potential to reduce Hb variability because the same dose given at extended dosing regimens could be less likely to produce Hb overshoot [10]. However, this hypothesis has not been confirmed probably because the initial dose of long acting ESAs in some pivotal clinical trials is relatively lower than the corresponding initial dose of the ESA in the comparator arm [11, 12]. Furthermore, comparisons of between subject Hb variability between ESAs in head-to-head randomized clinical trials (RCTs) are sparse and actually suggest that longer acting ESAs have similar between and within subject variability in Hb relative to other ESAs in patients not on dialysis [13]. In the absence of a head-to-head comparison in dialysis patients, an indirect comparison through a meta-analysis provides the best quantitative comparative information [14]. Our objective was to review systematically RCTs evaluating the different ESAs used to treat anaemia in dialysis patients to explore the effect of the ESA, their dosing schedule, route of administration and frequency of dose adjustments on the mean and between subject variability of both Hb and ESA dose. Notably, the fact that ESA dose is titrated to achieve the desired response reduces the sensitivity of the Hb as an endpoint to detect possible differences in efficacy across ESA. There-

fore, ESA dose is considered by the European Medicines Agency to be a co-primary endpoint for assessing biosimilars [15] and, consequently, we assessed both the mean values and the between patient variability in these two endpoints. Variability in ESA dose was assessed using coefficient of variation (CV) because it is a dimensionless number and overcame the problem of different dose units across ESAs.

Methods

We identified head-to-head RCTs conducted in adult patients with CKD, published between 1 January 2000 and 31 December 2009, comparing different ESAs [recombinant human epoetin (rHuEPO) alfa or beta, darbepoetin alfa, PEG-EPO, humanized rHuEPO epoetin delta or biosimilar epoetin (HX575, epoetin zeta)] for the treatment of anaemia (in correction or maintenance phase) with a Hb target between 9 and 13.5 g dl⁻¹ and a follow-up of at least 22 weeks. The RCTs search was conducted in BIOSIS Previews, Current Contents, EMBASE and Ovid MEDLINE (Table 1 and Figure 1).

We performed mixed effects meta-analyses on the Hb mean or SD, and the ESA dose mean or CV during the evaluation phase of the RCT. In studies in which Hb SD or ESA dose CV was not reported, it was estimated by dividing the range by 6 or the interquartile range (IQR) by 1.35 [16]. In studies in which mean Hb or mean ESA dose were not reported, the median value was used instead. In studies in which final mean Hb or mean ESA dose were not reported, the final values were estimated by adding the mean change to the mean baseline value, and the final SD was estimated by the square root of the final variance (variance of change minus variance of baseline value). All the mean doses were converted to IU kg⁻¹ week⁻¹ or µg kg⁻¹ week⁻¹, as applicable.

Since the correlation across studies between Hb SD and the CV of the ESA dose during the evaluation period of the RCT was limited (Figure 2), an independent analysis of Hb and ESA dose was deemed appropriate. The meta-analysis on ESA dose was done in a subset of studies with data available and analyzed both the mean and CV. The Hb mean and SD were also jointly analyzed.

The meta-analyses, conducted using NONMEM Version 7.1.0 (ICON Development Solutions, Ellicott City, MD, USA), used the following model:

$$P_{ijk} = P_k^* + \eta_{ik} + \varepsilon_{ijk}$$

where P_{ijk} is the point estimate for the k^{th} endpoint in the j^{th} arm in the i^{th} study, P_k^* is the typical value for the k^{th} endpoint across the arms and studies evaluated, η_{ik} represents the difference between the point estimate for the k^{th} endpoint in the i^{th} study and the typical value for the k^{th}

Table 1

Search strategy

Search #	Search description	Results
1	(hematocrit\$ or haematocrit or hemoglobin\$ or haemoglobin\$ or hgb or hb).ti,ab.	186 658
2	[darbepoietin or darbopoetin or aranesp or nesp or novel erythropoie\$ stimulating protein\$ or rHuEPO or EPOETIN\$ or erythropoietin or EPO or erythropoietin or erythropoiet\$ or darbepoetin\$ or (erythropoiesis adj2 stimulating adj2 factor\$) or erythropoiesis stimulating agent\$ or (erythropoietic adj2 factor\$) or (erythropoietic adj2 stimulat\$ adj2 factor\$) or epoetin\$ or hematopoietin\$ or haematopoietin\$ or hemopoietin\$ or haemopoietin\$ or ESA or biosimilar\$ or retacrit or binocrit or HX575 or cera or mircera or (methox\$ adj polyeth\$)].ti,ab.	20 871
3	(anem\$ or anaem\$).ti,ab.	143 401
4	(kidne\$ or renal\$ or nephro\$).ti,ab.	893 135
5	[dialy\$ or hemodial\$ or haemodial\$ or (periton\$ and dial\$)].ti,ab.	169 994
6	[random\$ or aleator\$ or (clinical adj2 trial) or (control\$ adj2 trial) or (compara\$ adj2 study) or (compara\$ adj2 trial)].ti,ab.	1 067 058
7	1 and 2 and 3 and 4 and 5 and 6	217
8	Remove duplicates from 7	130
9	Limit 8 to English language	115
10	Limit 9 to humans	115
11	Limit 10 to year = '2000–December 31 2009'	88

endpoint across the arms and studies evaluated, which is assumed to follow an independent random normal distribution with mean 0 and between clinical trial variance ω^2 and ε_{ijk} represents the difference between the point estimate for the k^{th} endpoint in the i^{th} study and the point estimate for the k^{th} endpoint in the j^{th} arm of the i^{th} study (between arms variability), which is assumed to follow an independent random normal distribution with mean 0 and variance σ^2/N_{ij} , where σ^2 represents the between subject variability and N_{ij} represents the sample size of the j^{th} arm in the i^{th} study.

On each endpoint, we explored the effect of the following variables: type of ESA (rHuEPO alfa or beta, darbepoetin alfa, PEG-EPO or other epoetins), route of administration (i.v. or s.c.), frequency of administration (two times a week or three times a week, weekly, every 2 weeks or monthly) and dose adjustment [weekly (followed by monthly), every 2 weeks, every 3 weeks, monthly or missing], baseline value of the dependent variable (quantitative variable), the study design (blinded vs. open) and type (correction vs. maintenance), Hb target and Hb monitoring frequency (weekly, every 2 weeks, monthly or missing). Epoetin delta, evaluated only in one study [17], was grouped with the two epoetin alfa biosimilars to reduce the number of comparison groups. The average of the target Hb range was evaluated on mean Hb and mean ESA dose, while the width of the target Hb range was evaluated on Hb SD and ESA dose CV.

The likelihood ratio test and the confidence interval of the point estimate at an acceptance P value of 0.05 were used to evaluate the presence of between trial heterogeneity and the effect of covariates on dependent outcomes. Graphical data visualization was conducted using S-Plus Version 8.0.4 (TIBCO Software Inc., Palo Alto, CA, USA).

Results

Haemoglobin analysis

The main characteristics of the studies selected (Figure 1) are presented in Table 2. Among the 4983 patients who participated in one of the 34 cohorts of the 16 selected studies, the pooled Hb mean and SD were 11.50 g dl⁻¹ (95% CI 11.30, 11.70) and 0.99 g dl⁻¹ (95% CI 0.88, 1.09), respectively. The heterogeneity test showed differences between the studies regarding the mean Hb (χ^2 39.78, $P < 0.001$), its SD (χ^2 33.77, $P < 0.001$) and both parameters simultaneously (χ^2 73.56, $P < 0.001$), which justified the use of a mixed effects model. The between trials variability was 3% and 19% for Hb mean and SD, respectively. The variability among cohorts within a clinical trial was higher than the variability between trials. Normalizing for a sample size of 150 patients per cohort, variability among cohorts within a clinical trial was 12% and 85% for Hb mean and SD, respectively. Excluding the studies in which Hb SD was not directly reported, but calculated for the analysis, did not change substantially the results.

No statistically significant differences in Hb mean and SD were observed according to the ESA, its route and frequency of administration, frequency of dose adjustment, study blinding, baseline value, frequency of Hb monitoring and target Hb range (Table 3 and Figure 3). Although no difference in mean Hb between correction and maintenance studies was observed, the pooled Hb SD in the 14 maintenance studies ($n = 4204$) was 0.94 g dl⁻¹ (95% CI 0.85, 1.01), significantly lower than that obtained in the two studies of anaemia correction ($n = 779$), 1.320 g dl⁻¹ (95% CI 1.316, 1.324) (Table 3 and Figure 2). This variable explained 32% of heterogeneity between studies in the Hb SD.

Figure 1

Flowchart of included studies. * Randomization according to administration of three iron formulations, treatment with oxpentifylline (anti-aggregant), ascorbic acid or folic acid supplementation, androgen administration, several diets or different dialysis fluids

Dose analysis

Among the 3700 patients included in the 13 selected studies (28 cohorts) with dosing data available (Table 2), the mean dose of rHuEPO, darbepoetin, PEG-EPO and other epoetins in the evaluation period was $104 \text{ IU kg}^{-1} \text{ week}^{-1}$ (95% CI 81, 127), $0.433 \mu\text{g kg}^{-1} \text{ week}^{-1}$ (95% CI 0.371, 0.495), $0.426 \mu\text{g kg}^{-1} \text{ week}^{-1}$ (95% CI 0.330, 0.522) and $115 \text{ IU kg}^{-1} \text{ week}^{-1}$ (95% CI 91, 139), respectively, and the CV of the dose was consistent across the ESA and estimated to be 76% (95% CI 67%, 85%). The heterogeneity test showed differences between the studies regarding the mean dose ($\chi^2 27.00$, $P < 0.001$), its CV ($\chi^2 17.06$, $P < 0.001$) and both parameters simultaneously ($\chi^2 43.85$, $P < 0.001$), which justifies the use of a mixed effects model. The between trials

variability was 33% and 13% for the ESA dose mean and CV, respectively. The variability among cohorts within a clinical trial was higher than the variability between trials. Normalizing for a sample size of 150 patients per cohort, variability among cohorts within a clinical trial was 172% and 86% for the ESA dose mean and CV, respectively. Excluding the studies in which ESA dose CV was not directly reported, but calculated for the analysis, did not substantially change the results.

No statistically significant differences in ESA dose mean and CV were observed according to the frequency of dose adjustment, study blinding and type and baseline values (Table 3). Neither statistically significant differences in the ESA dose mean nor CV were observed in relation to the

Table 2

Relevant characteristics of studies included in meta-analysis

Study (author, year)	ESA	Route	Dosage regimen	Type of study (C/M)	n	Target Hb (g dl ⁻¹)	Hb monitoring frequency	ESA dose adjustment frequency	Baseline Hb Mean (SD) (g dl ⁻¹)	Final Hb† Mean (SD) (g dl ⁻¹)	Baseline ESA dose Mean (CV)	Final ESA dose‡ Mean (CV)
Krivoshiev <i>et al.</i> , 2010* [37]	BS EPO-α	s.c.	QW/TIW	M	154	10.0–12.0	NR	NR	10.56 (1.35)	10.94 (0.84)	NR	97 IU kg ⁻¹ week ⁻¹ (0.972)
Nagaya <i>et al.</i> , 2010 [38]	DA	s.c.	QW/TIW	M	165	10.0–12.0	NR	NR	10.40 (1.43)	11.02 (0.94)	NR	86 IU kg ⁻¹ week ⁻¹ (0.907)
		i.v.	QW	M	19	10.0–13.0	QW	Q3W	11.20 (0.40)	10.90 (0.90)	0.43 µg kg ⁻¹ DW week ⁻¹ (0.442)	0.49 µg kg ⁻¹ DW week ⁻¹ (0.469)
		i.v.	Q2W	M	20	10.0–13.0	QW	Q3W	11.00 (0.40)	11.20 (0.90)	0.49 µg kg ⁻¹ DW week ⁻¹ (0.449)	0.91 µg kg ⁻¹ DW week ⁻¹ (0.637)
Haag-Weber <i>et al.</i> , 2009† [39, 40]	BS	i.v.	TIW	M	207	10.5–11.5	Q2W	Q2W	11.70 (0.93)	11.85 (0.94)	91 IU kg ⁻¹ week ⁻¹ (0.520)	87 IU kg ⁻¹ week ⁻¹ (0.531)
	EPO-α	i.v.	TIW	M	118	10.5–11.5	Q2W	Q2W	12.00 (0.88)	12.06 (0.92)	88 IU kg ⁻¹ week ⁻¹ (0.548)	78 IU kg ⁻¹ week ⁻¹ (0.582)
Li <i>et al.</i> , 2008 [41]	DA	s.c.	QW/Q2W	M	18	9.5–12.5	Q4W	Q4W	9.98 (0.76)	10.46 (0.87)	0.33 µg kg ⁻¹ week ⁻¹ (0.539)	0.38 µg kg ⁻¹ week ⁻¹ (0.664)
	rHuEPO	s.c.	QW/BIW	M	19	9.5–12.5	Q4W	Q4W	9.66 (0.78)	9.78 (0.88)	70 IU kg ⁻¹ week ⁻¹ (0.291)	80 IU kg ⁻¹ week ⁻¹ (0.316)
Locatelli <i>et al.</i> , 2008 [42]	EPO-α/DA	i.v.	QW/BIW/TIW	M	68	11.0–13.0	Q4W	Q4W	11.57 (0.67)	11.64 (0.67)	98 IU kg ⁻¹ week ⁻¹ (0.508)	95 IU kg ⁻¹ week ⁻¹ (NR)
	EPO-α	i.v.	QW	M	213	11.0–13.0	Q4W	Q4W	11.57 (0.71)	10.92 (0.65)	101 IU kg ⁻¹ week ⁻¹ (0.440)	126 IU kg ⁻¹ week ⁻¹ (NR)
Canada <i>et al.</i> , 2008 [43]	peg-EPO-β	i.v.	Q2W	M	123	10.0–13.5	QW	Q4W	12.00 (0.70)	12.10 (1.00)	0.495 µg kg ⁻¹ week ⁻¹ (0.453)	0.355 µg kg ⁻¹ week ⁻¹ (0.740)
	DA	i.v.	QW/Q2W	M	126	10.0–13.5	QW	QW-Q2W	11.90 (0.60)	11.80 (1.00)	0.445 µg kg ⁻¹ week ⁻¹ (0.707)	0.405 µg kg ⁻¹ week ⁻¹ (0.907)
Krivoshiev <i>et al.</i> , 2008† [44]	BS	i.v.	QW/TIW	C	300	11.0–12.0	QW	Q4W	8.07 (0.79)	11.61 (1.27)	NR	182 IU kg ⁻¹ week ⁻¹ (0.648)
	EPO-α	i.v.	QW/TIW	C	298	11.0–12.0	QW	Q4W	8.04 (0.79)	11.63 (1.37)	NR	166 IU kg ⁻¹ week ⁻¹ (0.661)
Spinowitz <i>et al.</i> , 2008 [45]	peg-EPO-β	s.c./i.v.	Q2W	M	123	10.0–13.5	QW	Q4W	11.80 (0.65)	11.93 (1.05)	0.405 µg kg ⁻¹ week ⁻¹ (0.494)	0.405 µg kg ⁻¹ week ⁻¹ (0.717)
	EPO-α	s.c./i.v.	QW/TIW	M	133	10.0–13.5	QW	QW-Q4W	11.88 (0.67)	11.86 (1.03)	945 IU kg ⁻¹ week ⁻¹ (1.124)	945 IU kg ⁻¹ week ⁻¹ (0.993)
Sulowicz <i>et al.</i> , 2007 [11]	peg-EPO-β	s.c.	Q4W	M	153	10.0–13.5	QW	Q4W	11.58 (0.72)	11.46 (0.99)	0.435 µg kg ⁻¹ week ⁻¹ (0.493)	0.545 µg kg ⁻¹ week ⁻¹ (0.784)
	peg-EPO-β	s.c.	Q2W	M	154	10.0–13.5	QW	Q4W	11.70 (0.72)	11.70 (1.04)	0.425 µg kg ⁻¹ week ⁻¹ (0.493)	0.395 µg kg ⁻¹ week ⁻¹ (0.754)
	EPO-α/EPO-β	s.c.	QW/TIW	M	167	10.0–13.5	QW	QW-Q4W	11.64 (0.70)	11.52 (1.07)	875 IU kg ⁻¹ week ⁻¹ (0.741)	795 IU kg ⁻¹ week ⁻¹ (0.808)
Klinger <i>et al.</i> , 2007 [12]	peg-EPO-β	i.v.	Q2W	C	135	11.0–13.0	QW	Q4W	9.39 (0.88)	12.09 (1.35)	0.205 µg kg ⁻¹ week ⁻¹ (0)	0.305 µg kg ⁻¹ week ⁻¹ (0.839)
	rHuEPO	i.v.	TIW	C	46	11.0–13.0	QW	QW-Q4W	9.40 (0.82)	11.96 (1.11)	1205 IU kg ⁻¹ week ⁻¹ (0.062)	745 IU kg ⁻¹ week ⁻¹ (0.972)
Martin, 2007† [17]	BS	i.v.	TIW	M	491	10.0–12.0	Q4W	Q4W	11.16 (0.77)	11.57 (1.07)	NR	190 IU kg ⁻¹ week ⁻¹ (NR)
	EPO-α	i.v.	TIW	M	175	10.0–12.0	Q4W	Q4W	11.13 (0.77)	11.56 (0.98)	NR	188 IU kg ⁻¹ week ⁻¹ (NR)
Levin <i>et al.</i> , 2007 [18]	peg-EPO-β	i.v.	Q2W	M	188	10.0–13.5	QW	Q4W	11.99 (0.62)	11.88 (1.08)	0.655 µg kg ⁻¹ week ⁻¹ (0.296)	0.375 µg kg ⁻¹ week ⁻¹ (0.937)
	peg-EPO-β	i.v.	Q4W	M	172	10.0–13.5	QW	Q4W	11.86 (0.64)	11.87 (0.99)	0.645 µg kg ⁻¹ week ⁻¹ (0.888)	0.565 µg kg ⁻¹ week ⁻¹ (0.747)
	rHuEPO	i.v.	QW/BIW/TIW	M	180	10.0–13.5	QW	QW-Q4W	11.96 (0.62)	11.87 (0.85)	1195 IU kg ⁻¹ week ⁻¹ (0.903)	1345 IU kg ⁻¹ week ⁻¹ (0.823)
Mitrescu <i>et al.</i> , 2006 [46]	EPO-β	s.c.	QW	M	101	10.0–12.0	Q4W	Q4W	11.32 (0.77)	11.38 (0.79)	72 IU kg ⁻¹ DW week ⁻¹ (0.488)	72 IU kg ⁻¹ DW week ⁻¹ (0.429)
	EPO-β	SC	Q2W	M	102	10.0–12.0	Q4W	Q4W	11.38 (0.85)	11.41 (0.88)	71 IU kg ⁻¹ DW week ⁻¹ (0.455)	68 IU kg ⁻¹ DW week ⁻¹ (0.569)
Nissenon <i>et al.</i> , 2002† [47]	DA	i.v.	QW	M	121	9.0–13.0	QW	Q2W	11.20 (0.42)	11.24 (1.02)	0.90 µg kg ⁻¹ week ⁻¹ (0.780)	0.77 µg kg ⁻¹ week ⁻¹ (0.878)
	EPO-α	i.v.	TIW	M	240	9.0–13.0	QW	Q2W	11.20 (0.50)	11.11 (0.96)	182 IU kg ⁻¹ week ⁻¹ (0.814)	195 IU kg ⁻¹ week ⁻¹ (0.938)
Vanrenterghem <i>et al.</i> , 2002 [48]	rHuEPO	s.c./i.v.	QW/TIW	M	112	9.0–13.0	QW	Q2W	11.00 (0.50)	11.00 (0.71)	NR	NR
	DA	s.c./i.v.	QW/Q2W	M	224	9.0–13.0	QW	Q2W	11.00 (0.50)	11.05 (0.62)	NR	NR
Weiss <i>et al.</i> , 2000 [49]	EPO-β	s.c.	QW	M	88	10.0–13.0	QW	Q4W	11.40 (0.60)	11.20 (1.20)	102 IU kg ⁻¹ week ⁻¹ (0.696)	103 IU kg ⁻¹ week ⁻¹ (0.660)
	EPO-β	s.c.	BIW/TIW	M	30	10.0–13.0	QW	Q4W	11.20 (0.60)	11.20 (1.20)	109 IU kg ⁻¹ week ⁻¹ (0.449)	109 IU kg ⁻¹ week ⁻¹ (0.523)

All studies (except when otherwise indicated) were open label; for comparison purposes, mean weekly dose kg⁻¹ is shown in all studies; in studies in which mean dose kg⁻¹ was not reported, it was estimated by dividing the mean weekly dose by the mean weight of the cohort (or by a mean weight of 70 kg, if the mean weight was missing); in studies in which SD was not reported, it was estimated by dividing the range by 6 or the interquartile range by 1.35; in studies in which mean dose was not reported, the median value was used; in studies in which final dose was not reported, but both the baseline value and the change during the study were available, the final dose was estimated by adding the mean change to the mean baseline dose, and the final standard deviation was estimated by the square root of the final variance (variance of change minus variance of baseline dose); BIW, twice weekly; BS, biosimilar of epoetin alfa; C, correction phase; CV, coefficient of variation; DA, darbepoetin alfa; DW, dry weight; EPO, epoetin; M, maintenance phase; NR, Not reported; peg-EPO, pegylated epoetin; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, monthly; QW, once weekly; rHuEPO, EPO-α/EPO-β; TIW, three times per week; †Observer-blind study, ‡Double-blind study, §Mean values during the evaluation period, §Median dose.

Figure 2

Scatter plot showing lack of correlation between the coefficient of variation of the ESA dose and Hb SD by study type: maintenance (■, black circles) and correction (■, grey circles, also indicated by C). The circle size is proportional to the sample size in each study arm

route and frequency of administration (Table 3). However, in stratifying by the ESA, the route of administration was significantly associated with the mean dose of rHu-EPO (χ^2 8.43, d.f. 2, $P = 0.015$). The pooled mean i.v. dose of rHuEPO ($n = 672$) was $121 \text{ IU kg}^{-1} \text{ week}^{-1}$ (95% CI 97, 145), which was 32% (95% CI 14%–50%) higher than the pooled mean s.c. dose of rHuEPO ($n = 882$). Furthermore, frequency of administration was significantly and negatively associated with the PEG-EPO mean dose (χ^2 13.36, d.f. 1, $P < 0.001$). The pooled mean dose of PEG-EPO every 2 weeks ($n = 723$) was $0.383 \mu\text{g kg}^{-1} \text{ week}^{-1}$ (95% CI 0.290, 0.476), was significantly lower than that obtained for monthly dosing ($n = 325$), $0.546 \mu\text{g kg}^{-1} \text{ week}^{-1}$ (95% CI 0.415, 0.677). During the assessment period in Levin *et al.*'s study [18], the median doses for PEG-EPO after dose titration were $57 \mu\text{g}$ every 2 weeks and $175 \mu\text{g}$ monthly. In Sulowicz *et al.*'s study [11], during the evaluation period, the median dosages of PEG-EPO were $56 \mu\text{g}$ every 2 weeks and $150 \mu\text{g}$ monthly. Thus, extending the dosing interval of PEG-EPO from every 2 weeks to monthly was associated with an increase of 42.6% (95% CI 37.4%, 47.8) in the dose. The effect of the route of administration on rHuEPO dose and the dosing frequency on PEG-EPO dose explained about 41% of the variability between cohorts of selected studies in relation to the mean ESA dose.

Hb monitoring frequency and target Hb range were significantly associated with ESA dose CV, but not with mean ESA dose (Table 3). The pooled mean of the ESA dose CV with weekly Hb monitoring ($n = 2816$) was 80% (95% CI 74, 87). Relative to weekly Hb monitoring, the ESA dose CV was significantly reduced by 32% (95% CI 27, 38) and 38% (95% CI 32, 44) with every 2 weeks ($n = 325$) and monthly ($n = 240$) Hb monitoring, respectively. This variable

explained 75% of heterogeneity between studies. Furthermore, the pooled mean of the ESA dose CV for a width of target Hb range of 3 g dl^{-1} was estimated to be 80% (95% CI 74, 85). For each 1 g dl^{-1} decrease in width of the target Hb range, a 10% (95% CI 5, 16) relative decrease in ESA dose CV was found. This variable explained 52% of heterogeneity between studies in the ESA dose CV.

The combined effect of the Hb monitoring frequency and the width of the target Hb range on the ESA dose mean and CV (Figure 4) was able to explain completely the heterogeneity between studies, and reduced the variability by 6% and 9%, respectively. The pooled mean ESA dose CV with weekly Hb monitoring and a width of target Hb range of 3 g dl^{-1} was 80% (95% CI 78, 83). The ESA dose CV was significantly reduced by 17% (95% CI 15, 20) and 32% (95% CI 30, 34) with biweekly and monthly Hb monitoring relative to weekly Hb monitoring, respectively. In addition, for each 1 g dl^{-1} decrease in width of the target Hb range, a 9% (95% CI 7, 11) relative decrease in the ESA dose CV was found.

Discussion

Despite a U-shaped relationship between absolute Hb levels and mortality risk in haemodialysis patients has been reported [19], very few studies have related Hb variability at the population level with clinical outcomes. A recent analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that between subject Hb variability at facility level was strongly associated with within patient Hb variability, and found substantially higher mortality rates for patients receiving dialysis in facilities with larger inter-patient Hb variation, defined as the Hb SD values [20]. However, Hb values observed in DOPPS were obtained from clinical practice, with different anaemia management protocols between centres, and thus are not directly comparable with our analysis of ESA administration in clinical trials.

To our knowledge, we present the first work systematically analyzing the influence of the variables related to ESA dosing on the Hb SD and the ESA dose CV at the population level, using pooled data from head to head RCTs. This methodology has been previously applied to other drug classes and provided additional insights in comparing different treatment effects [21–24]. The overall Hb SD estimate from the RCTs included in the present meta-analysis was lower than the Hb SD reported in observational studies in haemodialysis patients treated with ESA. This is not unexpected, considering the added attention and necessary adherence to ESA dosing protocol prescribed in the RCT, as well as the selection of patients who are generally healthier and less prone to hospitalization and other inter-recurrent events than the general dialysis population, which includes a much wider spectrum of patients. Therefore, data from head to head RCTs are more sensitive to

Table 3

Effect of each of the covariates tested on the Hb mean or SD, and on the mean ESA dose or CV of ESA dose, using a random effects model

Covariate	Hb mean			Hb SD			Mean of ESA dose			CV of ESA dose		
	χ^2	d.f.	P	χ^2	d.f.	P	χ^2	d.f.	P	χ^2	d.f.	P
Type of ESA (rHu-EPO alfa/beta; darbepoetin alfa; PEG-rHu-EPO beta; biosimilar)	4.13	3	0.248	4.52	3	0.243	Not applicable*			1.40	3	0.704
Route of administration (intravenous; subcutaneous; both)	3.33	2	0.189	1.68	2	0.431	5.10	2	0.078	0.79	2	0.672
Dosing regimen (BIW/TIW; BIW/TIW/QW; QW; QW/Q2W; Q2W; Q4W)	8.60	5	0.126	6.16	5	0.291	1.21	4	0.876	7.69	5	0.174
Frequency of ESA dose adjustment (QW followed by Q4W; Q2W; Q3W; Q4W; missing)	5.27	4	0.261	4.05	4	0.400	4.15	4	0.386	5.71	4	0.222
Baseline value of dependent variable	0.41	1	0.523	0.30	1	0.582	1.05	1	0.305	0.11	1	0.742
Study design (blinded; open)	0.67	1	0.412	3.10	1	0.078	1.30	1	0.253	0.23	1	0.630
Study type (correction; maintenance)	2.16	1	0.141	9.62	1	0.002	0.81	1	0.369	0.05	1	0.828
Average/Width of target Hb range†	3.23	1	0.072	1.06	1	0.304	0.73	1	0.393	5.34	1	0.021
Hb monitoring frequency (QW; Q2W; Q4W; missing)	6.00	3	0.112	2.93	3	0.403	2.33	3	0.507	13.25	3	0.004

BIW, twice weekly; CV, coefficient of variation; d.f., degrees of freedom; DA, darbepoetin alfa; EPO, epoetin; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; peg-EPO, pegylated epoetin; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, monthly; QW, once weekly; rHuEPO, EPO- α /EPO- β ; TIW, three times per week. *Not applicable because the lack of conversion of units between different ESAs; †Average target Hb range was assessed as covariate for the Hb mean and mean of ESA dose and width of target Hb range was assessed as covariate for the Hb SD and CV of ESA dose.

detect differences in Hb and ESA doses during its evaluation phase that could potentially be attributed to specific PK/PD properties of ESAs because, to a certain extent, randomization creates balance between the treatment arms (in terms of comorbidity and potential intercurrent events), thereby reducing the potential for differential influence of these factors when comparing across treatment arms [6–8, 25].

Our results do not suggest any relevant influence of the type of ESA, its route of administration, dosing frequency or dose adjustment frequency on mean Hb or between subject Hb variability, which suggests that intrinsic factors associated with the disease and not included in the present analysis must be involved. Notably, we have not noticed any influence of longer acting ESA administration on between subjects Hb variability, thereby not confirming previous theoretical hypotheses about its potential to reduce Hb variability [10]. However, the studies of anaemia correction showed higher variability than studies performed in patients with ESA maintenance treatment. Since the evaluation period of the two correction studies included in the meta-analysis was 24 weeks, we hypothesize that probably more than 6 months are needed to stabilize Hb levels in anaemic CKD patients on dialysis initiating ESA treatment.

Significant differences in the mean ESA dose at the evaluation period of head-to-head RCTs were found across the rHuEPO route of administration and PEG-EPO frequency of administration. The pooled mean of rHuEPO weekly s.c. dose during the evaluation phase of the RCTs was 32% (95% CI 14%–50%) less than the pooled mean of rHuEPO weekly i.v. dose. This result is consistent with the

outcome of RCTs comparing rHuEPO i.v. and s.c. routes [26]. Furthermore, the mean PEG-EPO monthly dose was 42% higher than the corresponding every 2 weeks dose, which was expected given the PEG-EPO PK/PD modelling results previously published [27]. This finding is also similar to that observed for darbepoetin alfa in the Patronus study [28] in switching from every 2 weeks to monthly (off-label use in dialysis patients) following i.v. dosing and, therefore, is a common phenomenon for both drugs [28], and raises the question as to whether monthly administration of ESA is cost-effective at the doses evaluated in dialysis patients included in the current meta-analysis.

No significant differences in ESA dose CV were found according to the evaluated variables, except for width of target Hb range and Hb monitoring frequency. It is expected that frequent Hb monitoring should contribute to reduce the variability in ESA and, indirectly, ESA labels reflected this phenomenon by recommending higher frequency of Hb monitoring after an ESA dose change. On the other hand, at frequencies of Hb monitoring higher than the ESA dosing frequency, the Hb cycling phenomenon become evident and it may contribute to the net increase in the ESA dose CV as shown in this analysis. Although it seems that a statistically significant reduction in Hb SD at the population level can be achieved with a narrow target Hb range [20, 29, 30], we could not confirm these findings probably because the target Hb range was very similar across all the studies included [only 2 out of 34 cohorts had a narrow range width (1 g dL⁻¹)] or the Hb SD is not as sensitive as ESA dose CV to detect the target Hb range effect on the variability. The relationship between ESA dose

Erythropoiesis stimulating agent

Route of administration

Dosing regimen

Figure 3

Hb SD stratified by ESA, route of administration and dosing interval. The black squares are proportional to the square root of the sample size in each subgroup. The figures on the right-hand side represent mean (95% CI). BIW two times a week, TIW three times a week, QW weekly, Q2W every 2 weeks, Q4W monthly

Figure 4

Relationship between the coefficient of variation of the ESA dose and the amplitude of the target Hb range width stratified by the Hb monitoring frequency. The circle size is proportional to the sample size in each study arm and the lines represent the relationship established in the current meta-analysis. —, monthly Hb sampling; —, biweekly Hb sampling; —, weekly Hb sampling; —, missing Hb sampling

CV and the width of target Hb range could also be an artefact of using data at the population level.

The strengths of our analysis are a systematic search with duplicate data extraction and quantitative analysis of the mean and between subject variability of both Hb and ESA dose. The main limitation is that the between patient variability on both Hb and ESA dose was analyzed at trial level, which may not reflect the within subject variability [31]. In a meta-analysis, data are combined from trials that differ in drug treatment, patient population characteristics and study design properties. This can lead to heterogeneity in the treatment effect across trials if these factors have an impact on the relative treatment effect between active and control arms. This is addressed by the inclusion of between trial random effects and explanatory trial level covariate relationships [32]. We observed significant heterogeneity across studies in the four parameters analyzed, which was reduced by including the significant variables. We have not analyzed the influence of other important variables related to management of ESA treated patients, such as iron administration, because the specific iron treatment was not consistently standardized and/or reported across trials. However, in the 12 out of 34 cohorts with data available (35%), the percentage of patients receiving iron was quite similar (range 73%–100%, median 87%, 25th/75th percentiles 83%–92%). The difference between the USA and the EU in managing anaemia in dialysis patients could not be evaluated because several multicentre studies were conducted in the USA, the EU and also other countries. In dealing with summary level data, it is not possible to assess the effect of individual patient specific factors, such as comorbid conditions and intercurrent events. Consequently, we restricted our analysis to RCTs in order to mini-

mize the potential confounding effect of these covariates and account for the correlation across arms within a clinical trial, via mixed effect modelling with trial as a nested variable because between trial heterogeneity was limited compared with between arms heterogeneity. For these reasons, the effect of these covariates (if any) is expected to be limited [33, 34].

Regarding data on EPO doses, mean values were available in 32 out of 34 (94%) analyzed cohorts and CVs could be calculated in 28 cohorts (82%). We considered that this sample was representative enough. In addition, the obtained results were quite precise, which implies that they only would change with the addition of missing data if the few studies without available information had completely different mean EPO doses and CVs than the rest (i.e. missing not at random). The probability of this happening is rather low. Thus, the decision of not taking them into account caused some power loss (not relevant with the large sample size remaining), but it is improbable that biased our conclusions. Finally, it may not be possible to extrapolate our findings on clinical trials to the real-life setting.

In conclusion, Hb and ESA dose variability at the population level are not associated with the type of ESAs used to treat anaemia secondary to CKD in patients on dialysis, their dosing interval, route of administration or frequency of ESA dose adjustment, except for higher dose requirements for rHuEPO dosing through i.v. route relative to s.c. dosing and PEG-EPO monthly dosing compared with biweekly dosing. Therefore, the intrinsic PK/PD characteristics of ESAs do not correlate directly with between subject Hb variability after ESA dose is titrated. These results suggest that the between subject variability of Hb and the ESA dose observed in ESA-treated CKD patients on dialysis is an intrinsic factor associated with the disease and the comorbidities associated with each patient, independent of the type of ESA used, its dosing schedule and its PK/PD properties. The main strategies currently recommended to limit this unavoidable variability in chronic haemodialysis patients are to individualize ESA treatment according to CKD comorbidities and to use iron dosing algorithms [35], together with a narrow target Hb range and appropriate Hb monitoring [36].

Competing Interests

This study was supported by Amgen SA, Spain. JJ. Pérez-Ruixo, M. Cucala-Ramos and E. García-Gonzalo were employees of Amgen SA, Spain at the time the analysis was conducted. M. Cucala-Ramos is a former employee of Amgen SA, Spain. B. Del Val Romero and Neus Valveny are employees of Trial Form Support SL, Spain. JJ. Pérez-Ruixo, M. Cucala-Ramos and E. García-Gonzalo have shares in Amgen SA. The authors have no other conflicts of interest to declare.

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