Nephrol Dial Transplant (2000) 15 [Suppl 4]: 20–32

Nephrology
Dialysis
Transplantation

European Best Practice Guidelines 6–8
Assessing and optimizing iron stores

Iain C. Macdougall, Walter H. Hörl, Claude Jacobs, Fernando Valderrábano, Ima Parrondo, Karen Thompson and Saskia Cremers

Results

Key points from the EBPG

- All chronic renal failure patients must be iron replete to achieve and maintain the target haemoglobin (Hb).
- Adequate iron status is defined as: serum ferritin $\geqslant 100$ μg/l, hypochromic red cells $< 10\%$ [transferrin saturation (TSAT) $> 20\%$]. To achieve these targets, the population medians will be: serum ferritin 200–500 μg/l and hypochromic red cells $< 2.5\%$ (TSAT 30–40%).
- Almost all haemodialysis patients will require intravenous iron.

Key results from ESAM

- During any given month of the survey, between 15 and 22% of haemodialysis and between 41 and 45% of peritoneal dialysis patients had absolute iron deficiency.
- 41% of patients receiving epoetin in the correction phase had iron stores monitored less frequently than is recommended by EBPG.
- Almost 19% of haemodialysis and 34% of peritoneal dialysis patients received no iron supplementation during the 6-month study.
- Of those patients with absolute iron deficiency receiving no iron supplementation in the first month of the study, 60.4% were still receiving no iron 5 months later.
- In haemodialysis patients, both the mean haemoglobin levels and the epoetin dose required to achieve these haemoglobin levels were significantly different across the three categories of iron status; patients with adequate iron status reached a higher haemoglobin level with a lower epoetin dose.

The role of iron is crucial to red cell production and to the epoetin response, as the need for available iron is increased due to enhanced erythropoietic activity [1,2]. While underdialysis (Kt/V < 1.2) and poor nutritional status (based on low serum albumin concentrations) were identified in the 1997 ESRD Core Indicators Project paper as having a negative impact on the correction of anaemia with epoetin [3], iron deficiency, whether absolute or functional, was clearly implicated as the major factor responsible for a suboptimal response to epoetin therapy [4]. Conversely, inadequate iron stores may result in higher dose requirements of epoetin as physicians strive to achieve the target haemoglobin.

Although no definitive test is available, iron deficiency or iron overload commonly are measured by the serum ferritin concentration (expressed in μg/l) as an index of iron stores, and/or the percentage of hypochromic red cells in circulation (as an index of the availability of these stores) [1]. Since the required auto-analysers for measuring hypochromic red cells are not always available, the percentage of transferrin saturation (TSAT) is used as an appropriate substitute, although it must be noted that the TSAT level is prone to diurnal variation and may not always be a reliable indicator [5].

Guideline 6 provides the minimally acceptable levels for adequate iron status: serum ferritin $\geqslant 100$ μg/l with hypochromic red cells $< 10\%$ (or TSAT $> 20\%$). Optimal levels are defined as: serum ferritin of 200–500 μg/l with hypochromic red cells $< 2.5\%$ (or TSAT of 30–40%). Two additional categories of iron status were also used for the ESAM analysis: (i) absolute iron deficiency: serum ferritin < 100 μg/l; and (ii) functional iron deficiency: serum ferritin $\geqslant 100$ μg/l and TSAT $< 20\%$.

The prevalence of iron deficiency

While 15.3–21.7% of haemodialysis patients were classified as having absolute iron deficiency, the percentage of peritoneal dialysis patients with absolute iron deficiency in any given month ranged from 40.9 to 44.5%. Table 14 shows monthly iron status for haemodialysis and peritoneal dialysis patients in the maintenance phase of epoetin therapy. Between 57.5 and 64.6% of haemodialysis patients had an adequate iron status in any given month, while 45.0–49.5% of peritoneal dialysis patients had an adequate iron status.

Given the importance of serum ferritin as a marker of iron deficiency, we examined the distribution of month 6 serum ferritin levels for haemodialysis and

Table 14. Distribution of patients by iron status and type of dialysis

	Haemodialysis patients in maintenance phase of epoetin treatment			Peritoneal dialysis patients in maintenance phase of epoetin treatment		
	Adequate iron status % (*n*)	Functional iron deficiency % (*n*)	Absolute iron deficiency % (*n*)	Adequate iron status % (*n*)	Functional iron deficiency % (*n*)	Absolute iron deficiency % (*n*)
Month 1	57.5 (3657)	21.2 (1350)	21.3 (1358)	46.2 (326)	13.6 (96)	40.2 (284)
Month 2	62.7 (2548)	19.2 (782)	18.1 (736)	49.5 (248)	10.8 (54)	39.7 (199)
Month 3	62.3 (2661)	20.4 (871)	17.2 (736)	48.2 (239)	12.1 (60)	39.7 (197)
Month 4	63.8 (2655)	20.1 (837)	16.0 (667)	45.0 (217)	13.1 (63)	41.9 (202)
Month 5	64.6 (2454)	19.9 (754)	15.5 (588)	47.4 (225)	12.8 (61)	39.8 (189)
Month 6	63.9 (2348)	21.4 (786)	14.8 (543)	47.3 (182)	13.5 (52)	39.2 (151)

peritoneal dialysis patients (Figure 13). The results differ for the two modalities of dialysis. In the haemodialysis patients who had valid month 6 data, 37.5% had serum ferritin levels of 200 µg/l or less. Of the peritoneal dialysis patients, 60.3% had ferritin levels in this range. The haemodialysis patients were distributed more evenly across all serum ferritin categories. The observed difference in serum ferritin levels between haemodialysis and peritoneal dialysis patients was statistically significant ($\chi^2 = 334.797$, df = 7, $P < 0.001$).

Bivariate distributions of hypochromic red cells by haemoglobin, serum ferritin and TSAT are provided for months 1, 3 and 6 in Figures 14 and 15.

Iron status and haemoglobin

In haemodialysis patients, both the mean haemoglobin levels and the epoetin dose required to achieve these haemoglobin levels were significantly different across the three categories of iron status (see bottom of Figure 16). Results for peritoneal dialysis patients are more difficult to interpret, as (somewhat surprisingly) patients with absolute iron deficiency had slightly higher haemoglobin values than did those with either functional iron deficiency or adequate iron status (see bottom of Figure 17). The explanation for this unexpected finding remains unclear.

Table 15 shows the numbers and percentages of both haemodialysis and peritoneal dialysis patients achieving adequate iron status who had haemoglobin levels of $\leqslant 11.0$ g/dl at months 1, 3 and 6. The percentage of patients having adequate iron status in a given month but who did not achieve a haemoglobin of at least 11.0 g/dl in that month ranged from 44.9 to 48.6% of haemodialysis patients and from 42.0 to 45.7% of peritoneal dialysis patients. Differences in the distribution of patients achieving a haemoglobin of at least 11.0 g/dl between haemodialysis patients and peritoneal dialysis patients were not significant for any month. When the definition of iron adequacy was modified to include the measurement of hypochromic red cells

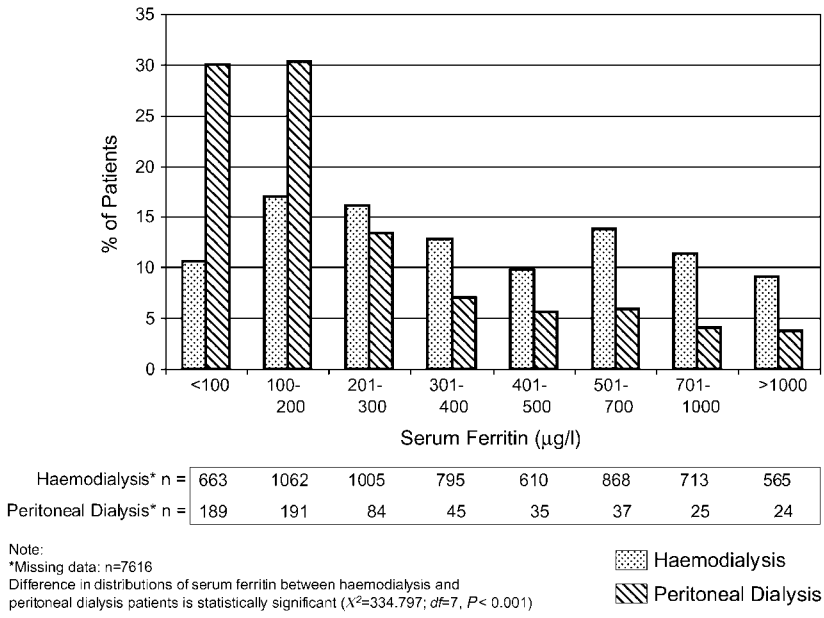

Fig. 13. Distribution of month 6 serum ferritin levels.

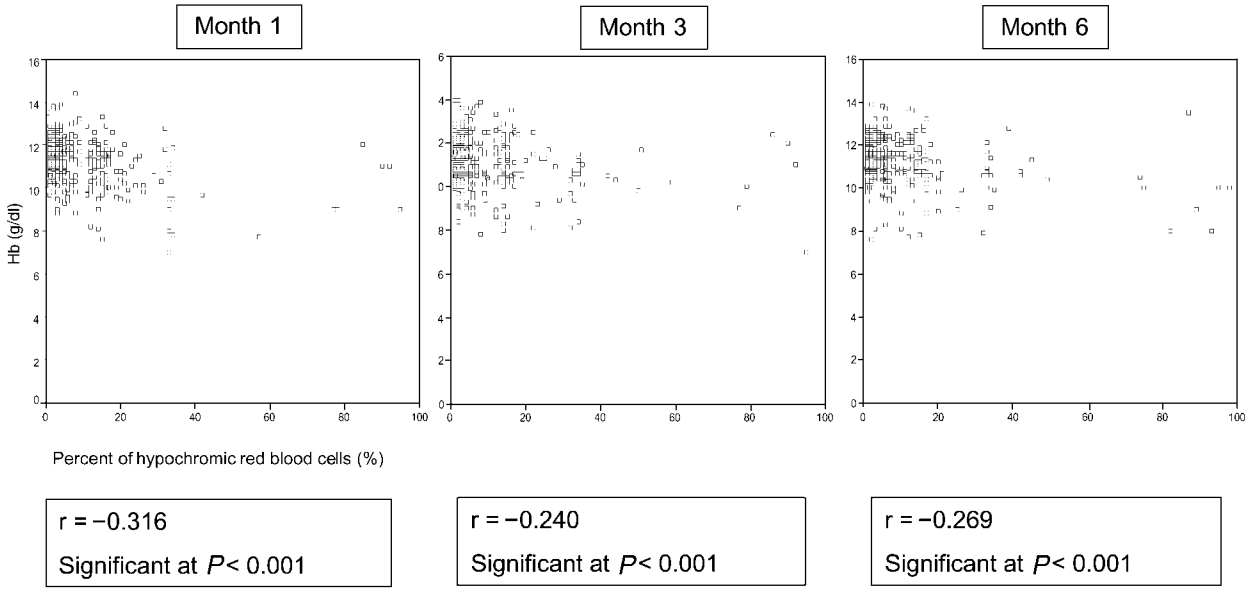

Fig. 14. Hypochromic red cells by Hb (months 1, 3 and 6).

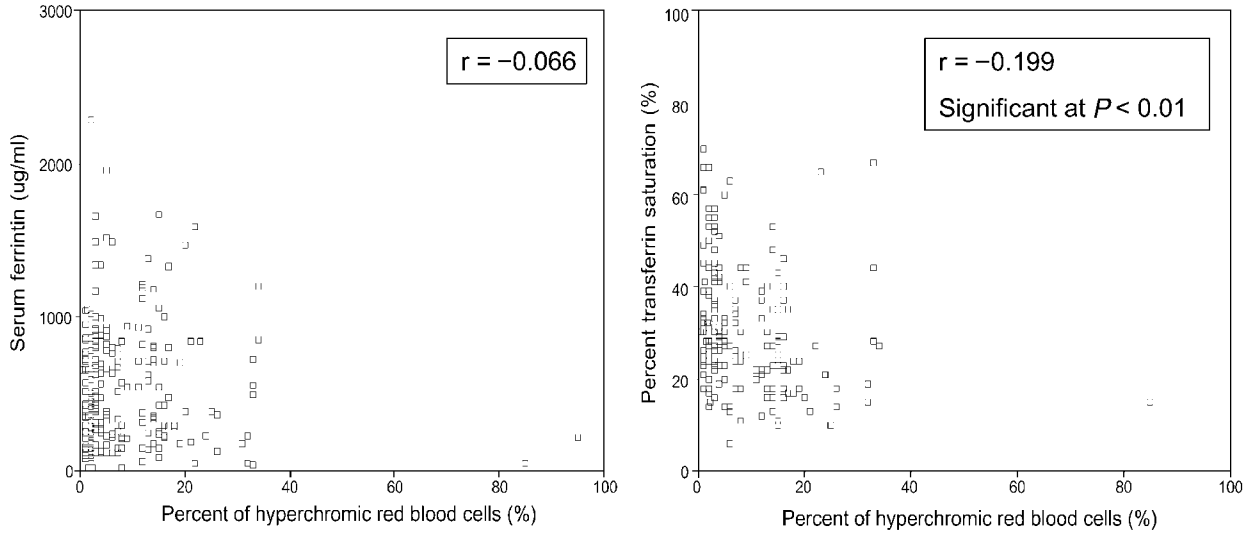

Fig. 15. Hypochromic red cells by serum ferritin (month 1) and by transferrin saturation (month 1).

(<10%), the percentage of haemodialysis patients failing to achieve a haemoglobin of 11.0 g/dl decreased to levels ranging from 34.3 to 43.4%.

Iron status and epoetin dose

Since an adequate iron supply is essential for optimum red cell production, it might be expected that iron deficiency would be associated with higher epoetin dose requirements. The mean epoetin doses used and the achieved haemoglobin levels are shown in Table 16 and in Figures 16 and 17. For months 1, 3 and 6, significant differences in epoetin dose were observed among the three iron status categories for haemodialysis patients (month 1: $F=24.74$, df$=2$, 7461, $P<0.001$; month 3: $F=21.19$, df$=2$, 4868, $P<0.001$; month 6: $F=39.17$, df$=2$, 4106, $P<0.001$; see Figure 16). Patients with adequate iron status consistently had the lowest epoetin dose requirements. Though less pronounced, similar findings were recorded for peritoneal dialysis patients at months 1 and 6 (respectively, $F=5.83$, df$=2$, 827, $P<0.01$; $F=4.01$, df$=2$, 433, $P<0.05$) but not in month 3 ($F=1.86$, df$=2$, 563, $P=$NS; see Figure 17). Again, in all 3 months, the lowest epoetin doses were seen in patients with adequate iron status.

We also examined patients at the extremes of the iron status continuum, specifically those with optimal iron status (serum ferritin between 200 and 500 µg/l and TSAT between 30 and 40%), and those with inadequate iron status (serum ferritin <100 µg/l)

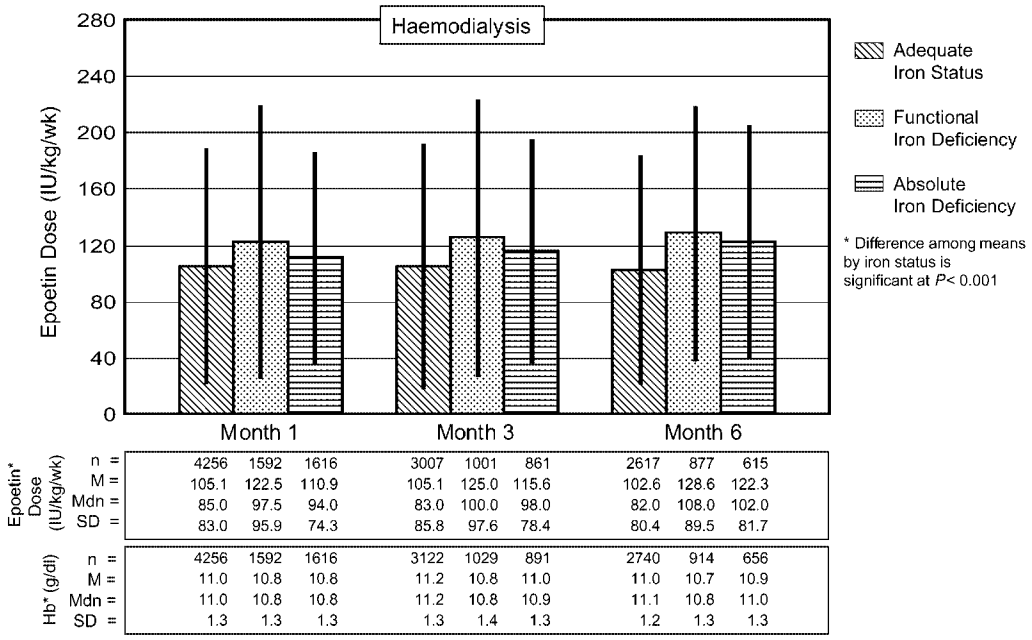

Fig. 16. Epoetin dose by adequacy of iron status (months 1, 3 and 6).

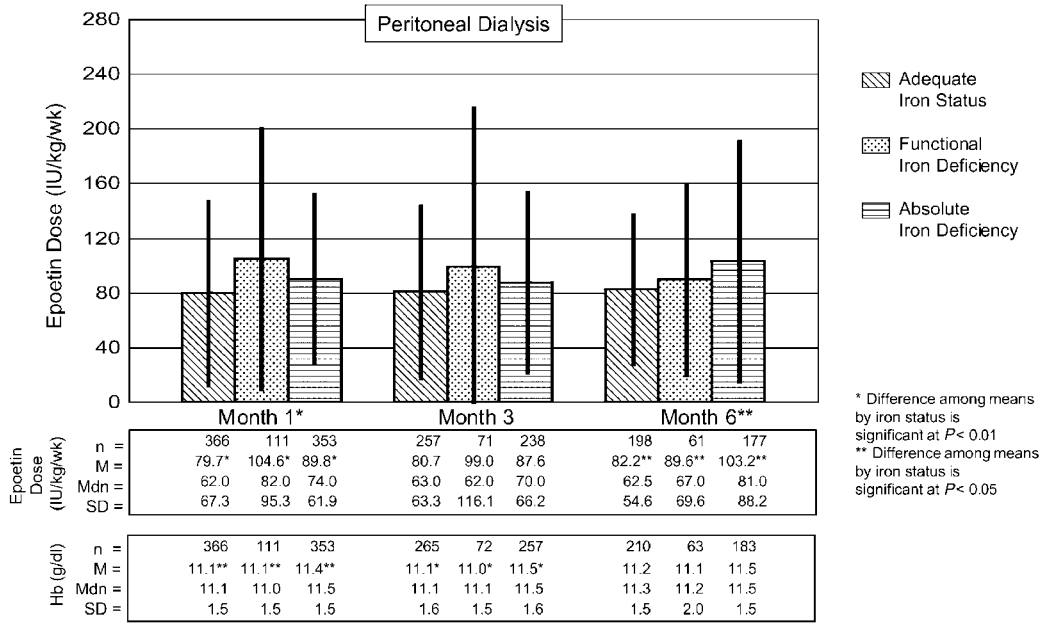

Fig. 17. Epoetin dose by adequacy of iron status (months 1, 3 and 6).

(Tables 17 and 18, Figure 18). Patients with inadequate iron status received significantly higher doses of epoetin at months 2–6 (respectively $t=-3.29$, df$=1094$, $P<0.01$; $t=-2.63$. df$=1150$, $P<0.01$; $t=-3.61$, df$=1081$, $P<0.001$; $t=-2.73$, df$=1036$, $P<0.01$; $t=-5.68$, df$=809.935$, $P<0.001$) although this difference was not found at month 1 ($t=-1.17$, df$=1684$, $P=$NS). Patients with optimal iron status achieved significantly higher haemoglobin levels at months 1–5 ($t=3.21$, df$=1684$, $P<0.01$; $t=2.08$, df$=1094$, $P<0.05$; $t=3.06$, df$=644.268$, $P<0.05$; $t=4.06$, df$=782.928$, $P<0.001$; $t=2.84$, df$=665.961$, $P<0.01$), but not at month 6 ($t=1.46$, df$=692.565$, $P=$NS).

Iron status monitoring

EBPG 7C defines the minimum frequency of iron status monitoring during the correction phase of epoetin therapy: every 4–6 weeks in patients not receiving iron, and every 3 months in patients receiving i.v. iron. Following attainment of the target haemoglobin, iron

Table 15. Patients achieving adequate iron status[a] by Hb, months 1, 3 and 6

	Haemodialysis % (*n*)	Peritoneal dialysis % (*n*)	All patients % (*n*)
Mean month 1 Hb g/dl)			
<11.0 g/dl	48.6 (1521)	45.7 (96)	48.4 (1617)
⩾11.0 g/dl	51.4 (1607)	54.3 (114)	51.6 (1721)
Mean month 3 Hb g/dl)			
<11.0 g/dl	44.9 (1056)	44.6 (75)	44.8 (1131)
⩾11.0 g/dl	55.1 (1298)	55.4 (93)	55.2 (1391)
Mean month 6 Hb g/dl)			
<11.0 g/dl	45.6 (1024)	42.0 (68)	45.3 (1092)
⩾11.0g/dl	54.4 (1223)	58.0 (94)	54.7 (1317)

[a]Adequate iron status was defined as serum ferritin of ⩾100 μg/ l and TSAT of ⩾20%.

status should be monitored every 3–6 months (EBPG 7B). Figure 19 shows the frequency of iron monitoring for patients in both the correction and the maintenance phases of epoetin therapy; 41% of patients starting epoetin therapy had their iron status monitored less frequently than is recommended by EBPG (for a description of the definition of correction and maintenance phases used in this study, see Figure 28).

Iron supplementation

EBPG 8B states that almost every haemodialysis patient will require at least one dose of i.v. iron every 2 weeks. Furthermore, peritoneal dialysis patients not receiving epoetin may have their iron stores maintained with oral iron, but patients receiving epoetin will require i.v. iron supplementation.

The use of iron supplementation in ESAM is shown in Figure 20. Nearly 20% of haemodialysis patients and 34% of peritoneal dialysis patients received no iron supplementation during the 6 months of the study, while ~80% of haemodialysis and 66% of peritoneal dialysis patients received iron supplementation for at least one out of the 6 months. However, only 27.0% of all patients received iron supplementation for *all* 6 months. Of those who did receive supplemental iron for all 6 months, 81.2% received only i.v. iron supplementation, 14.1% received only oral iron and 4.7% received a combination of i.v. and oral iron.

Changes in the route of iron supplementation for haemodialysis and peritoneal dialysis patients differed significantly from months 1 to 6, as shown in Table 19. For haemodialysis patients, the percentage of patients in the 'no iron' group increased from month 1 (39.8%) to month 6 (44.2%), while both the i.v. iron and oral iron groups decreased. For the peritoneal dialysis group, however, the percentage of patients receiving no iron remained fairly constant (50.0% at month 1 to 48.7% at month 6), while the percentage of patients receiving i.v. iron supplementation showed a slight increase. Figures 21–24 illustrate the distribution of iron status for haemodialysis and peritoneal dialysis patients in the maintenance phase of treatment. Figures 21 and 22 compare the iron status in dialysis patients who received iron supplementation throughout all 6 months of the survey with those who received no iron during this period. Haemodialysis patients generally showed less absolute iron deficiency compared with peritoneal dialysis patients, and they also had a higher proportion of adequate iron status. In both groups,

Table 16. Distribution of epoetin dose and Hb level for month 6

	Haemodialysis			Peritoneal dialysis			All patients		
	Epoetin dose (IU/kg/ week)	Hb (g/dl)	*n*	Epoetin dose (IU/kg/ week)	Hb (g/dl)	*n*	Epoetin dose (IU/kg/ week)	Hb (g/dl)	*n*
No iron in 6 months									
Adequate iron status	104.4	10.9	422	81.6	11.3	56	101.7	11.0	478
Functional deficiency	116.5	10.7	111	56.1	11.3	9	112.0	10.8	120
Absolute deficiency	119.1	10.6	86	86.4	11.8	41	108.5	11.0	127
Iron in all 6 months									
Adequate iron status	99.5	11.2	814	78.4	11.4	64	97.9	11.2	878
Functional deficiency	134.4	10.7	242	74.4	11.6	23	129.2	10.8	265
Absolute deficiency	120.0	11.0	127	103.8	11.4	53	115.2	11.1	180
I.v. iron in all 6 months[a]									
Adequate iron status	100.0	11.2	780	92.4	11.5	12	99.9	11.2	792
Functional deficiency	136.4	10.8	229	60.6	12.4	5	134.7	10.8	234
Absolute deficiency	127.4	11.2	89	83.4	11.0	5	125.1	11.2	94
Oral iron in all 6 months[a]									
Adequate iron status	88.1	10.7	34	75.1	11.3	52	80.3	11.1	86
Functional deficiency	99.1	9.7	13	78.2	11.3	18	87.0	10.6	31
Absolute deficiency	102.8	10.7	38	105.9	11.4	48	104.5	11.1	86

The sample includes only subjects with valid iron data at all 6months.
[a]I.v. iron all 6 months and oral iron all 6 months are subcategories of iron in all 6 months.

Table 17. Iron status, epoetin dose and mean haemoglobin, months 1–6

		Optimal iron status	Inadequate iron status
Month 1	Mean epoetin dose (IU/kg/week)	103.1	108.0
	Mean Hb (g/dl)[b]	11.1	10.9
	n	407	1279
Month 2	Mean epoetin dose[b] (IU/kg/week)	99.1	116.8
	Mean Hb (g/dl)[c]	11.1	10.9
	n	315	781
Month 3	Mean epoetin dose[c] (IU/kg/week)	97.6	111.4
	Mean Hb (g/dl)[b]	11.2	11.0
	n	314	838
Month 4	Mean epoetin dose[a] (IU/kg/week)	99.7	120.5
	Mean Hb (g/dl)[a]	11.2	10.9
	n	345	738
Month 5	Mean epoetin dose[b] (IU/kg/week)	103.0	118.9
	Mean Hb (g/dl)[b]	11.2	11.0
	n	314	724
Month 6	Mean epoetin dose[a] (IU/kg/week)	92.9	119.7
	Mean Hb (g/dl)	11.1	11.0
	n	307	664

[a]*t*-test comparing optimal iron status group with inadequate iron status group significant at $P<0.001$; [b]*t*-test comparing optimal iron status group with inadequate iron status group significant at $P<0.01$; [c]*t*-test comparing optimal iron status group with inadequate iron status group significant at $P<0.05$.

Table 18. Results of paired *t*-tests for differences between means: haemoglobin month 1 *vs* month 6, epoetin dose month 1 *vs* month 6

	Haemoglobin month 1 *vs* month 6	Epoetin dose month 1 *vs* month 6
Optimal iron status (month 1 and month 6) $n=49$	mean = 11.0 *vs* mean = 11.1 $t=-0.619$; df = 48; P = NS	mean = 89.5 *vs* mean = 81.0 $t=1.516$; df = 48; P = NS
Inadequate iron status (month 1 and month 6) $n=326$	mean = 10.7 *vs* mean = 11.0 $t=-3.191$; df = 325; $P<0.01$	mean = 107.9 *vs* mean = 113.5 $t=-1.742$; df = 325; P = NS

there were no obvious differences between the two cohorts of patients who received continuous iron and those who received no iron during all 6 months. Figures 23 and 24 compare patients who received only oral iron for all 6 months with those who received i.v. iron for all 6 months. The patterns of distribution are clearly different for haemodialysis and peritoneal dialysis patients. Haemodialysis patients who received only oral iron had a much higher incidence of absolute iron deficiency ($\sim$40% of the sample). A much lower incidence of absolute iron deficiency, $\sim$10–20%, occurred in those haemodialysis patients receiving i.v. iron continuously throughout the 6-month period. There was also a much higher incidence of adequate iron status in patients receiving regular i.v. iron ($\sim$60% of the sample). The same analysis was done in peritoneal dialysis patients (Figure 24), and results were similar, although perhaps less marked. Generally, patients who received i.v. iron throughout all 6 months had a lower incidence of absolute iron deficiency ($\sim$20–30%), whereas those receiving only oral iron for all 6 months had an incidence of absolute iron deficiency of $\sim$50%. The sample size of the peritoneal dialysis patients, however, was somewhat small, particularly in the cohort receiving regular i.v. iron.

Due to the fact that the iron status variable can be both an indicator of the need for iron supplementation and a consequence of iron supplementation, it is difficult to interpret these panel data. Instead, patterns of iron administration are more meaningful when cohort comparisons are made.

One cohort review that was conducted involved a sample of patients with absolute iron deficiency (serum ferritin <100 µg/l) who were receiving no iron supplementation at month 1 (33% of the total population of absolute iron-deficient patients). The cohort was followed up for months 2–6, and an alarmingly high proportion of patients still received no iron supplementation (71.7% at month 2, 65.3% at month 3, 64.1% at month 4, 61.1% at month 5 and 60.4% at month 6). The same data were evident in peritoneal dialysis patients. Although the sample size was small, 39.2% of patients with absolute iron deficiency were receiving no iron therapy at month 1; 87.8% of this sample were still receiving no iron at month 2, 83.6% were receiving no iron supplementation at month 3, 70.4% were receiving no iron at month 4, 65.2% were receiving no iron at month 5 and 63.2% were receiving no iron at month 6.

Figure 25 shows data from three cohorts of patients: (i) those taking no iron during all 6 months of the survey; (ii) those taking only oral iron during all 6 months; and (iii) those taking i.v. iron during all 6 months. No significant differences in the mean haemoglobin concentration were found among these three groups of patents; likewise, analyses of each of the cohorts in terms of their iron status did not reveal any significant differences. It is likely, therefore, that the major effect of adequacy of iron status is reflected more in the epoetin dose requirements rather than in the mean haemoglobin achieved. The problem also with this type of analysis is that it is difficult to know whether patients with absolute iron deficiency receiving i.v. iron are being prescribed the i.v. iron as a result of absolute iron deficiency (which would seem more likely), rather than *developing* absolute iron deficiency while on i.v. iron.

Infection and iron supplementation

In addition to haemoglobin and epoetin dose requirements, other outcomes of iron supplementation were examined, including the development of infections. Of those patients taking iron supplementation, oral and

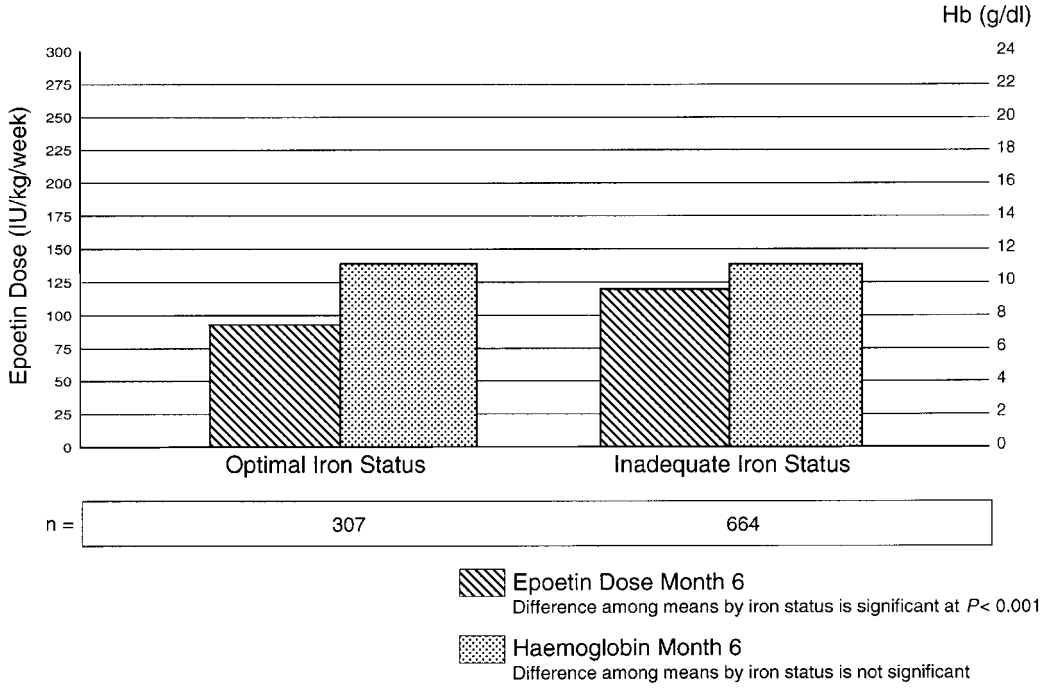

Fig. 18. Epoetin dose and Hb level (month 6) by iron status (month 6).

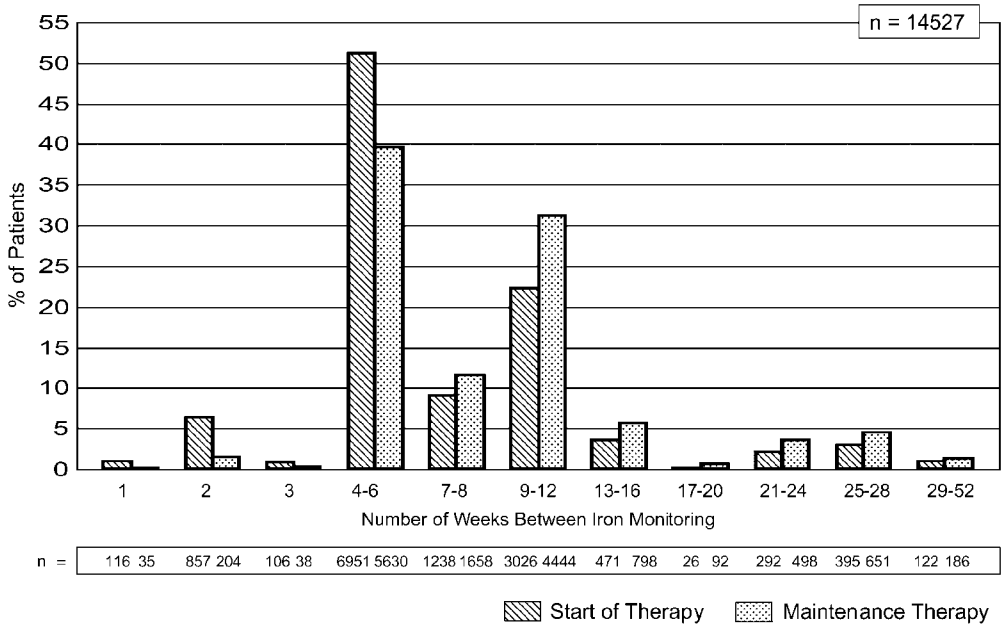

Fig. 19. Iron monitoring frequency.

i.v. administration routes were associated with similar infection rates (Figure 26). When the number of i.v. iron administrations per month was evaluated, there were no differences in the monthly infection rates between those who received $\geqslant 9$ and those who received $\leqslant 2$ administrations of i.v. iron. Similarly, differences in infection rates between patients receiving doses of i.v. iron of $\geqslant 300$ mg/month versus those receiving $\leqslant 100$ mg/month were not statistically significant [except in month 5 when patients receiving i.v. iron doses $\geqslant 300$ mg/month had an infection rate of 7.8% compared with 5.7% for those receiving i.v. iron doses $\leqslant 100$ mg/month ($\chi^2 = 5.06$, df = 1, $P < 0.05$)].

Figure 27 displays the incidence of infections in relation to the patients' serum ferritin levels. Three cohorts of patients were examined: (i) those with a serum ferritin < 500 μg/l; (ii) those with a ferritin between 500 and 800 μg/l; and (iii) those with a serum

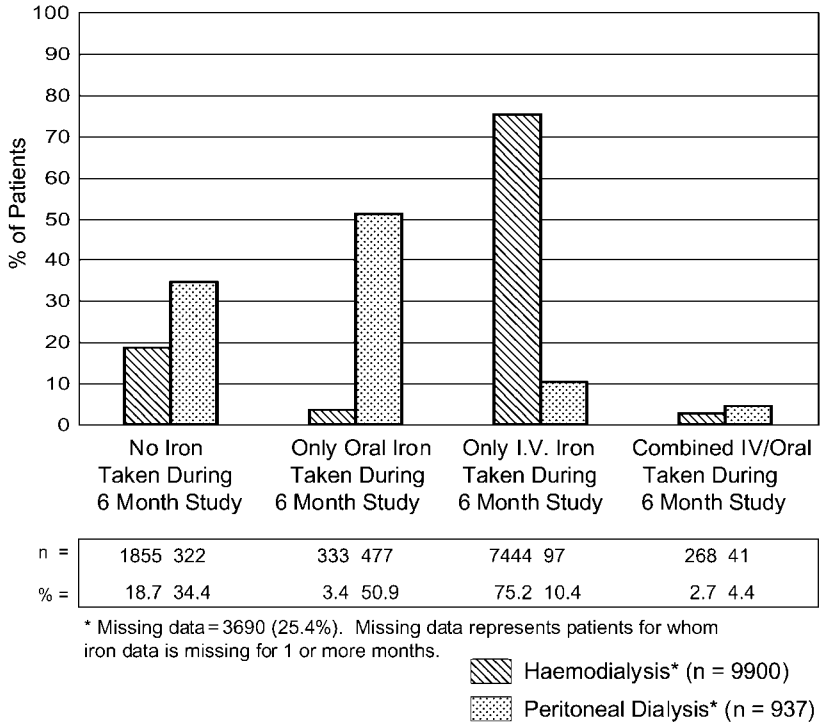

Fig. 20. Use of iron supplementation in dialysis patients.

Table 19. Administration route of iron in haemodialysis and peritoneal dialysis patients (months 1, 3 and 6)

Type of dialysis	Administration route	Month 1[a]		Month 3		Month 6[a]	
		n	%	*n*	%	*n*	%
Haemodialysis ($n=10\,694$)	No iron	4258	39.8	4521	42.3	4730	44.2
	i.v.	5953	55.7	5725	53.5	5555	51.9
	Oral	483	4.5	448	4.2	409	3.8
Peritoneal dialysis ($n=1015$)	No iron	508	50.0	513	50.5	494	48.7
	i.v.	69	6.8	76	7.5	77	7.6
	Oral	438	43.2	426	42.0	444	43.7

[a]The relationship is significant at $P<0.001$ for both haemodialysis and peritoneal dialysis.

ferritin >800 μg/l. The majority of patients had no infections reported, while $\sim 10\%$ of patients reported one infectious complication. There were very small numbers of patients developing more than one infection throughout the 6-month survey. There was no obvious relationship between the incidence of infectious disease and the serum ferritin, in that patients with iron overload (ferritin >800 μg/l) did not seem to have any significant increase in the risk of infection.

Comments

Effective iron management arguably is as important to the patient with renal anaemia as is administering epoetin therapy. There are two aspects to this topic: (i) monitoring iron status and reliably detecting absolute and functional iron deficiency; and (ii) adequate replacement with iron supplementation.

While it is now well established that iron deficiency is one of the most common causes of a suboptimal response to epoetin, and i.v. iron is effective in enhancing the erythropoietic response, it remains unclear what the best parameters are for monitoring iron status, and what should be the minimally acceptable levels for such parameters. A serum ferritin level >100 μg/l, TSAT $>20\%$ and hypochromic red cells $<10\%$ are the most commonly quoted thresholds for adequate iron status [1,2,6] and, in order to achieve these levels in a population of renal failure patients, it has been suggested that ferritin levels of between 200 and 500 μg/l, TSAT levels of between 30 and 40% and hypochromic red cells $<2.5\%$ should be targeted [6].

The results shown in Table 14 suggest that there are significant differences in iron status between haemodialysis and peritoneal dialysis patients. It would appear that the proportion of haemodialysis patients with adequate iron status is significantly greater than for

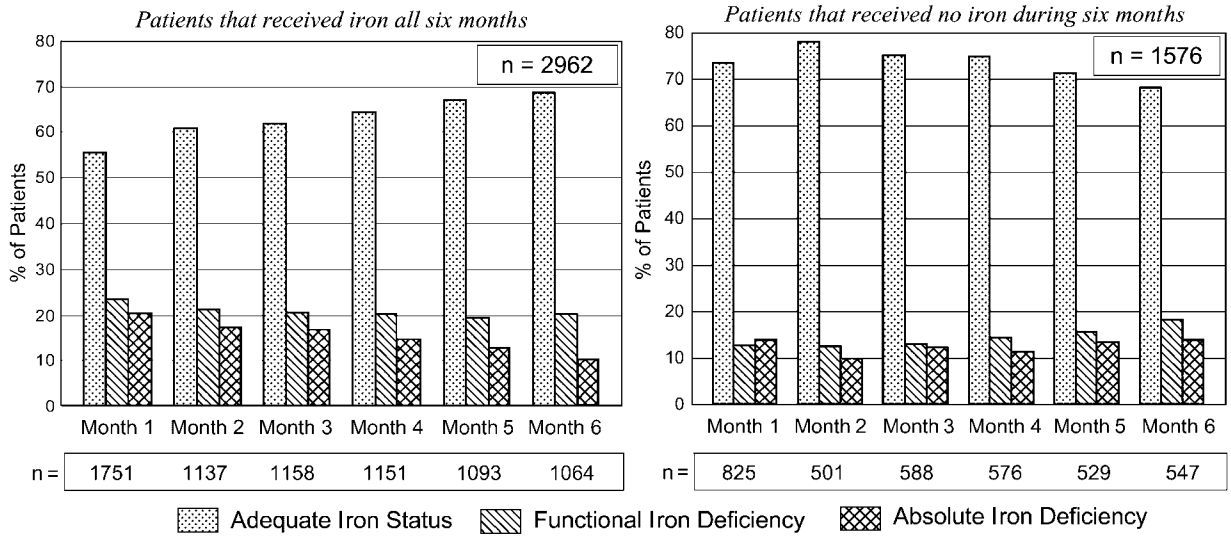

Fig. 21. Iron status of haemodialysis patients in the maintenance phase of treatment.

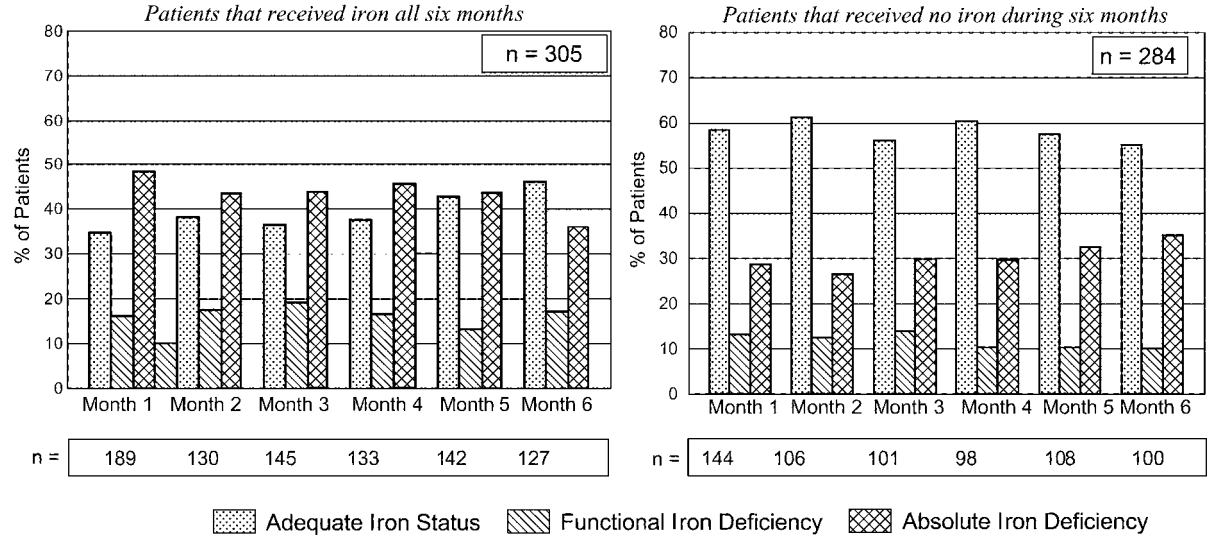

Fig. 22. Iron status of peritoneal dialysis patients in the maintenance phase of treatment.

peritoneal dialysis patients, the latter group having twice the proportion of patients with absolute iron deficiency ($\sim$40% compared with $<$20%). This is almost certainly due to the greater use of intravenous iron in haemodialysis patients, as shown, for example, in Figure 20.

Although the key messages regarding adequate iron status have been well publicized over the last decade or so, it is of some concern to see that this is somewhat lacking in so many patients in the survey, particularly since the deficit is so easily corrected. Figure 13 shows that just over 10% of haemodialysis and 30% of peritoneal dialysis patients have serum ferritin levels $<$100 μg/l at month 6, thus falling short of the recommendation in EBPG 6. A similar proportion of patients has borderline adequate iron stores of between 100 and 200 μg/l. It is also evident that the number of patients with iron overload (e.g. serum ferritin $>$1000 μg/l) is now significantly lower than in former times when regular blood transfusions were given. Clearly one might be less concerned if the patients who had inadequate iron status did in fact have adequate haemoglobin concentrations. Figure 25, however, indicates that the administration of iron is not related directly to achieved haemoglobin.

It is interesting that the patients who had regular monitoring of hypochromic red cells generally had higher levels of haemoglobin, serum ferritin and TSAT, in association with a higher epoetin dose. The most likely explanation for this is that these data come from units in which the overall management of the patient is more intensely focused. Thus, it is not the

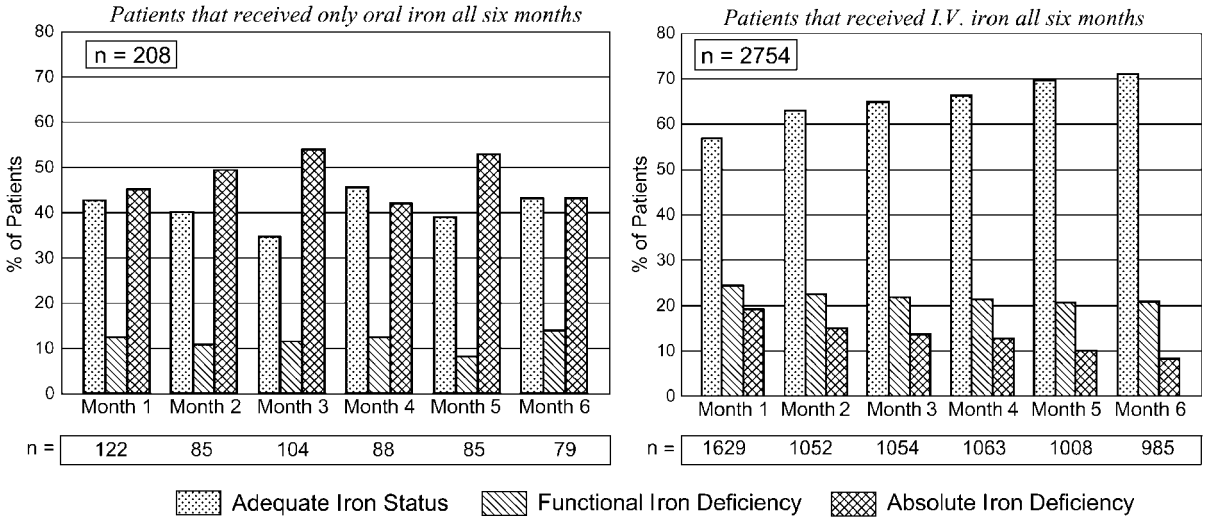

Fig. 23. Iron status of haemodialysis patients in the maintenance phase of treatment: oral and i.v. administration.

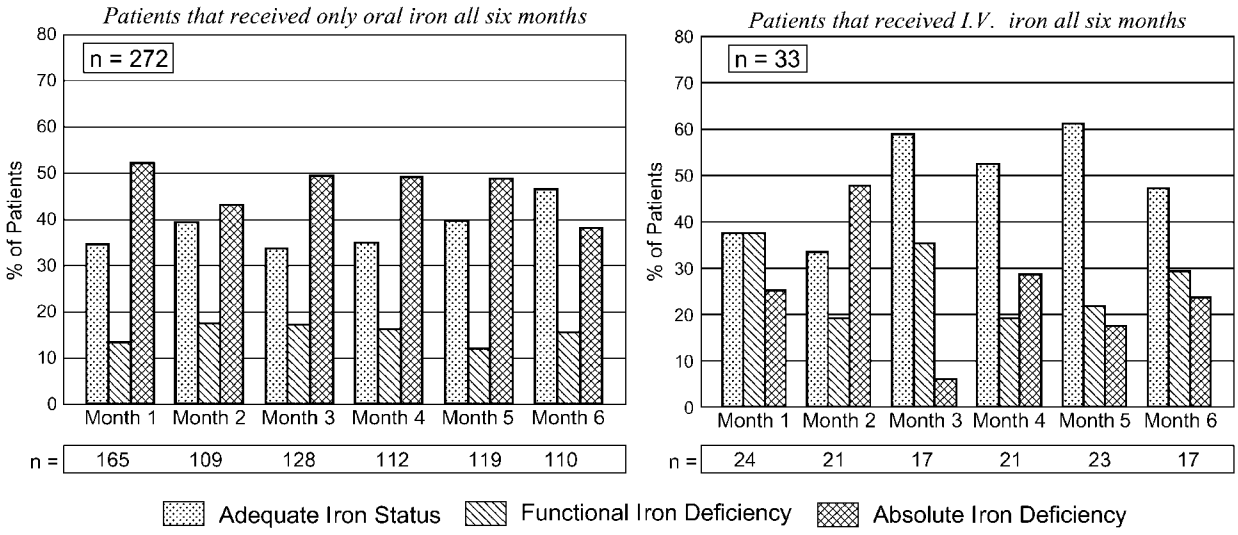

Fig. 24. Iron status of peritoneal dialysis patients in the maintenance phase of treatment: oral and i.v. administration.

measurement of hypochromic red cells *per se* that is producing better results, but this is acting as a marker for 'good quality' units.

It is not particularly surprising that there is no correlation between serum ferritin and the percentage of hypochromic red cells. Serum ferritin is primarily a reflection of iron stores, whereas the percentage of hypochromic red cells reflects the presence of functional iron deficiency. This can occur at all levels of serum ferritin, and the lack of any correlation has been found previously [7]. The significance of the weak negative correlation between haemoglobin and percentage hypochromic red cells is difficult to explain, and its clinical significance is somewhat unclear. The negative correlation between transferrin saturation and hypochromic red cells, seen in Figure 15, is similar to that described previously [7]. This indicates that as the percentage transferrin saturation decreases (in functional iron deficiency), the percentage of hypochromic red cells increases.

The frequency of iron monitoring was assessed in $>14\,500$ patients in the survey (Figure 19), and there is clearly some variability in this. The majority of units, however, seem to assess iron status every 4–6 weeks in the correction phase of epoetin therapy, and either every 4–6 weeks or 9–12 weeks in patients in the maintenance phase of treatment. There are still a large number of patients who are having their iron status assessed less frequently than is recommended by the EBPG.

The data in Figure 20 confirm that the majority of patients receive iron supplementation for at least 1 month during the 6 months surveyed. It is perhaps of some concern that 18.7% of haemodialysis patients and 34.4% of peritoneal dialysis patients received no iron supplementation during the 6 months of

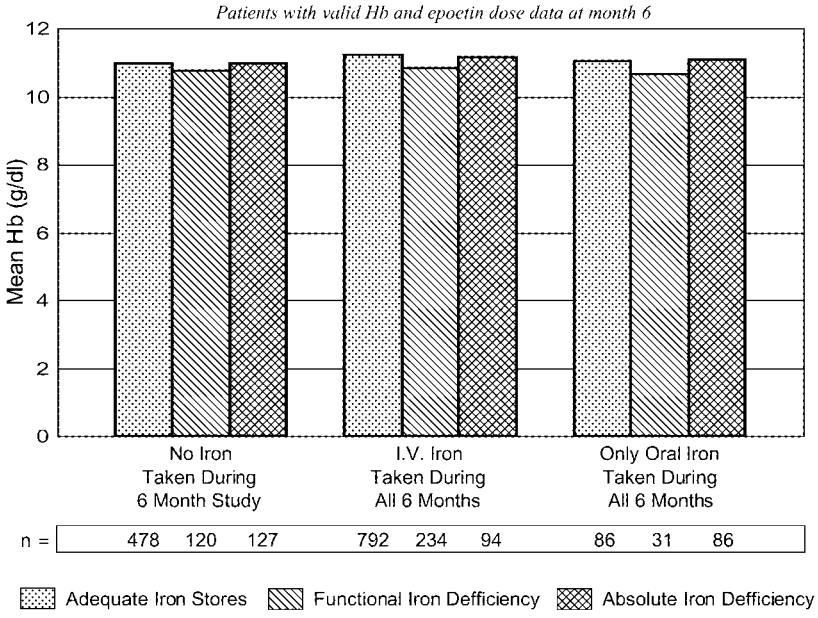

Fig. 25. Mean Hb level for patients by type of iron treatment and level of iron status.

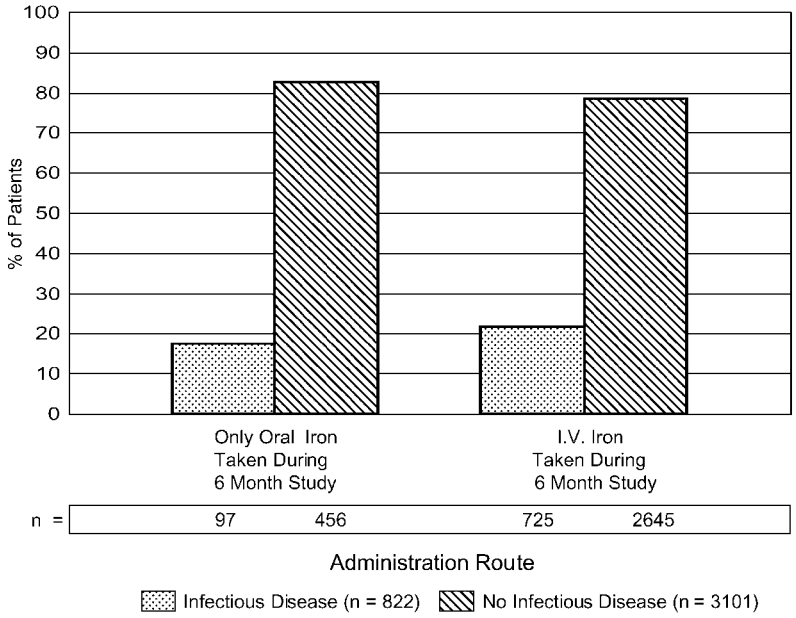

Fig. 26. Patients who had an infectious disease occurrence *vs* patients who did not have an infectious disease occurrence.

follow-up. This almost certainly represents suboptimal anaemia management, and hopefully this will improve. It is also contrary to the EBPG, which suggest that almost all haemodialysis patients require at least one dose of i.v. iron every 2 weeks. Furthermore, in a nationally representative database of US haemodialysed patients, 25% received no iron supplementation [3]. In the 27% of patients with overt iron deficiency defined by a TSAT $<20\%$ ($\sim$1350 patients), a quarter of them ($\sim$340 patients) received no iron, and half of them did not receive parenteral iron.

It is gratifying to see that the combined use of oral and i.v. iron is very limited, in line with the EPBG recommendations. There is no logic to this practice of joint use, since there will be negligible oral iron absorption in any patient receiving i.v. iron, and thus the patient is exposed to unnecessary gastrointestinal side effects. As expected, most of the haemodialysis patients were given i.v. iron while the peritoneal dialysis patients were maintained on oral iron if possible (Figure 20).

Taken in conjunction with Figures 23 and 24, the data also suggest that oral iron is not as effective at maintaining adequate iron status as i.v. iron. Although there are clearly logistical difficulties, it may be that

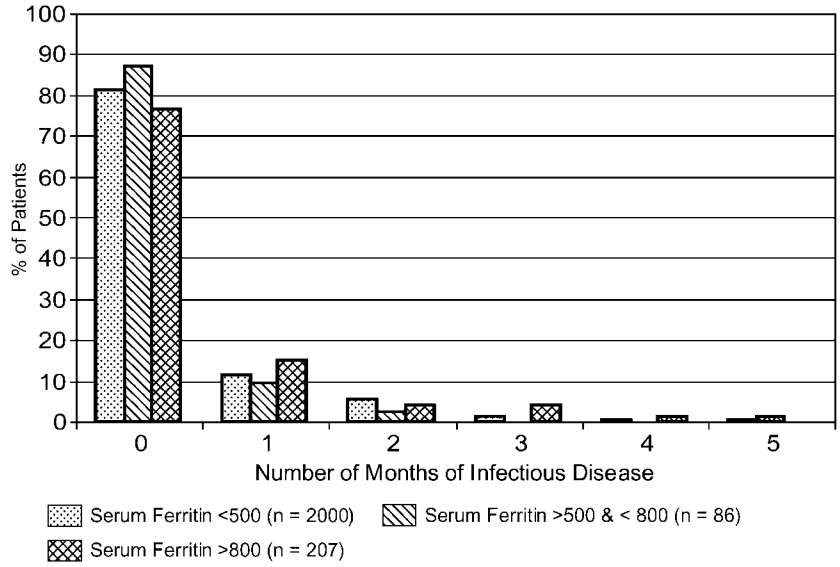

Fig. 27. Incidence of infectious diseases by serum ferritin.

greater use of i.v. iron is required in the peritoneal dialysis population than is being used currently.

The data in Figure 21 are somewhat difficult to interpret. There is a suggestion that patients who received iron in all 6 months of the survey had a lower proportion of adequate iron status. Patients who received no iron during the 6 months, however, seemed to maintain an adequate iron status, and this is almost certainly due to the fact that patients with adequate iron stores were not given iron supplementation rather than to the fact that patients not receiving any iron achieved adequate iron status. Also, in Figure 22, the proportion of peritoneal dialysis patients with inadequate iron status and absolute iron deficiency was significantly greater than that observed for haemodialysis patients (Figure 21). This again reflects the greater use of i.v. iron in the haemodialysis population.

There are some additional troubling findings regarding iron management: specifically, the results from cohorts of haemodialysis and peritoneal dialysis patients for which complete data on iron use are present for all 6 months of the survey. Of those with absolute iron deficiency and receiving no iron supplementation at month 1, 60.4% of haemodialysis patients and 63.2% of peritoneal dialysis patients were still receiving no iron 5 months later. Again, this is in contrast to the recommendations of EBPG which suggest that most haemodialysis patients will require i.v. iron supplementation every 2 weeks or so. This recommendation is for patients with all levels of adequacy of iron status, but it is clearly more pertinent for patients who have absolute iron deficiency. It is puzzling why some nephrologists have elected to leave so many patients with absolute iron deficiency with no iron supplementation over this 5-month follow-up period. Again, there is room for improvement in peritoneal dialysis patients.

While there are clearly limitations in monitoring the incidence of infectious diseases in this cohort sample, in the light of other published data [8–10] it was interesting to look for any relationship between the chances of developing an infection in relation to the serum ferritin level. No obvious relationship existed, although more rigorous scientific data are required to assess this more reliably.

In conclusion, whether the ESAM data are reassuring or not depends on whether you are an optimist or a pessimist. The optimist would conclude that iron status is being monitored fairly regularly, and i.v. iron is being used frequently. The pessimist would feel that since guidelines regarding iron management have been available for >10 years now, better results should be achieved. Particularly in the peritoneal dialysis population, there may be a need for greater use of i.v. iron, and hopefully ways can be found to solve the logistical problems associated with this.

Iron management remains fundamental to any patient receiving epoetin therapy, and hopefully the ESAM data provided in response to EBPG 6–8 will inspire us to continue our efforts to improve the clinical management of patients with renal anaemia.

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