

Original Article

Iron supplementation in haemodialysis—practical clinical guidelines

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Abstract

Background. The aim of this prospective study was to test a new protocol for iron supplementation in haemodialysis patients, as well as to assess the utility of different iron metabolism markers in common use and their 'target' values for the correction of iron deficiency.

Methods. Thirty-three of 56 chronic haemodialysis patients were selected for long-term (6 months) i.v. iron therapy at 20 mg three times per week post-dialysis based on the presence of at least one of the following iron metabolism markers: percentage of transferrin saturation (%TSAT) <20%; percentage of hypochromic erythrocytes (%HypoE) >10% and serum ferritin (SF) <400 µg/l. Reasons for patient exclusion were active inflammatory or infectious diseases, haematological diseases, psychosis, probable iron overload (SF ≥400 µg/l) and/or acute need of blood transfusion mostly due to haemorrhage and change in renal replacement treatment.

Results. More than half (51.8%) of the patients of our dialysis centre proved to have some degree of iron deficiency in spite of their regular oral iron supplementation. At the start of the study the mean haemoglobin was 10.8 g/dl and increased after the 6 months of iron treatment to 12.8 g/dl ($P < 0.0001$). The use of erythropoietin decreased from 118 units/kg/week to 84 units/kg/week. The criterion for iron supplementation with the best sensitivity/specificity relationship (100/87.9%) was ferritin <400 µg/l. Patients with ferritin <100 µg/l and those with ferritin between 100 µg/l and 400 µg/l had the same increase in haemoglobin but other parameters of iron metabolism were different between the two groups.

Conclusions. Routine supplementation of iron in haemodialysis patients should be performed intravenously. Target ferritin values should be considered individually and the best mean haemoglobin values were achieved at 6 months with a mean ferritin of 456 µg/l (variation from to 919 µg/l). The percentage of transferrin saturation, percentage of hypochromic erythrocytes and ferritin <100 µg/l, were not considered useful parameters to monitor routine iron

supplementation in haemodialysis patients. No significant adverse reactions to iron therapy were observed.

Key words: erythropoietin; ferritin; haemodialysis; iron; intravenous

Introduction

With the widespread utilization of rHuEpo in haemodialysis, prolonged or chronic iron overload and haemosiderosis have almost disappeared. Erythropoietin promotes the use of iron deposits in the bone marrow, and consequently iron deficiency is a frequent problem resulting in resistance to the full effect of rHuEpo. It is well known that a negative iron balance may occur—up to 2 g/year [1]—and it is not well established whether there is a compensatory increase in intestinal absorption in haemodialysis patients when they are iron deficient [2–5]. Oral supplementation is plagued by poor patient adherence due to frequent side-effects, and interference of other medication with the digestive absorption [6]. Several studies have demonstrated the utility of i.v. iron supplementation in correcting anaemia and sparing rHuEpo [7–10]. However the multiple publications evaluating the criteria to detect and to treat patients with iron deficiency and the several protocols adopted to correct this situation clearly show that there is no consensus [11–18].

We administered 20 mg iron i.v. post-dialysis on a long-term basis because it allows approximated continuous availability of iron to be incorporated into haemoglobin under the action of rHuEpo and allowed easy control to prevent the oversaturation of transferrin [19,20] and iron overload.

We evaluated rHuEpo dose and haemoglobin during long-term i.v. iron therapy for 6 months and evaluated the best markers to monitor this therapy. Prior to this study, iron status was assessed on a 3-month basis by serum ferritin (SF) and the percentage of transferrin saturation (%TSAT); iron supplementation was given orally as a routine and the i.v. route was reserved for severe cases of iron deficiency or gastrointestinal intolerance.

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Patients and methods

Study design

In a haemodialysis unit with 56 patients, 33 subjects meeting at least one of the following criteria: percentage of transferrin saturation (%TSAT) <20%; percentage of hypochromic erythrocytes (%HypoE) >10% and serum ferritin (SF) <400 µg/l, were prospectively selected to initiate iron i.v. therapy. The serum ferritin cut-off was arbitrarily chosen because there is no consensus regarding the target level of ferritin in the published literature [13–15]. In order to determine the level of ferritin under which there would be still response to iron, patients were divided into two groups based on ferritin level: Group I with baseline SF <100 µg/l and Group II with baseline SF ≥100 µg/l and <400 µg/l.

The other 23 patients were excluded because of active inflammatory or infectious disease (4), haematological disease (3—chronic lymphocytic leukaemia, aplastic anaemia, and thalassaemia major), psychosis (1), probable iron overload (SF ≥400 µg/l) and/or acute need of blood transfusion mostly due to haemorrhage (13) and change of renal replacement treatment (2).

In addition to the routine follow-up procedures of the unit, blood cell count with %HypoE, serum iron, transferrin and SF were evaluated in all patients.

We considered an increase of at least 1 g/dl of haemoglobin over the initial value as a positive response to iron therapy. We observed in our population of patients that this was the minimum change that made different two means of haemoglobin significant.

Patients

Thirty-three patients (13 females and 20 males) concluded the study. The aetiologies of renal failure were chronic glomerulonephritis 3, chronic pyelonephritis/interstitial nephritis 4, adult polycystic kidney disease 2, Alport syndrome 1, nephroangiokeratosis 10, renovascular hypertension 2, diabetes mellitus 3, Wegener granulomatosis 1, analgesic nephropathy 2, and unknown 5. Their mean age was 57.5±14.0 years and mean time on haemodialysis was 45.3±33.9 months. At the beginning of the study, the mean values of the parameters were haemoglobin 10.8±1.0 g/dl, serum ferritin 137±92.3 µg/l, %transferrin saturation 27.4±7.9, and %hypochromic erythrocytes 5.6±3.8. Erythropoietin consumption was 118.2±53.2 units/kg/week. Twenty patients of 33 were on oral iron before the study.

Selection of patients for i.v. iron treatment out of the total 56 of the unit

Twelve patients had percentage of transferrin saturation <20%. All of them had SF less than 400 µg/l and only one had a percentage of hypochromic erythrocytes above 10%. One patient was excluded because of probable iron overload (SF=877 µg/l) and recent transfusions, two had haematological diseases, and one had psychiatric disease.

Hypochromic erythrocytes were above 10% in seven patients. Every patient had SF <400 µg/l and one had transferrin saturation <20%. Four patients were excluded based on probable iron overload (SF=877 µg/l) and recent transfusions (1), active inflammatory/infectious disease (2), and haematological disease (1).

Target ferritin levels are not well established [13–15].

Therefore we included all patients with SF <400 µg/l and without the above referred exclusion criteria, enrolling 33 patients into the study. If we had used a more restrictive criterion (SF <100), 16 patients would not have been treated.

Iron administration and rHuEpo adjustment

Iron saccharate (Venofer®) 20 mg, diluted in 10 cc of saline was administered by the i.v. route during the last 10 min of each dialysis treatment. All patients discontinued oral iron. Criteria to stop the i.v. iron administration were allergic reaction; intolerable symptoms like metal taste, pruritus, paraesthesia, numbness; hepatic, pancreatic, or cardiac dysfunction, and increase of SF to values over 600 µg/l. With reference to the latter, iron was resumed if SF fell to values less than 400 µg/l.

The dose of rHuEpo was adjusted whenever haemoglobin increased to values above 12.5 g/dl.

Laboratory monitoring

The percentage of transferrin saturation was determined using the following formula: %TSAT=(serum iron×100)/(transferrin×1.27). The percentage of hypochromic erythrocytes was calculated by determining the haemoglobin concentration of each erythrocyte using light-scattering equipment with two reading angles (Technicon Mod. H2 System). Samples were processed within 60 min. Serum ferritin was determined by enzyme-linked fluorescent assay (ELFA). Serum iron was determined by colorimetric method without deproteinization (FerroZine® chromogen). All these assays were subjected to daily standard procedures of quality control.

Statistics

To study values with a normal distribution, we used Student's paired *t* test to compare values in the same patient. To compare groups of patients, non-paired *t* test was used. If the values did not have a normal distribution, as in the case of serum ferritin and rHuEpo consumption, non-parametric tests were done, either Wilcoxon signed rank test in the same patient or Mann-Whitney rank sum test for groups of patients. Values are expressed as mean±SD. Regression analysis was used to establish correlation between the various iron metabolism markers.

Results

Utility of iron markers

Iron deficiency was diagnosed in every case showing an increase of at least 1 g/dl in the haemoglobin level after i.v. iron treatment; 29 of 33 treated patients responded positively.

Table 1 shows a sensitivity of 100% and a specificity of 87.9% in the patients selected by ferritin <400 µg/l. The overlapping of these criteria must be emphasized, i.e. all patients with SF <400 includes all the patients with %TSAT <20 and %HypoE >10.

Haemoglobin evolution

There was a progressive increase in the mean value of haemoglobin from 10.8 g/dl±1.0 at the beginning to

Table 1. Sensitivity and specificity of iron markers

(n)	False neg. (n)	False pos.	Sensitivity (%)	Specificity (%)
SF <100 (n=17)	15	3	51.7	82.3
SF <400 (n=33)	0	4	100	87.9
%TSAT <20 (n=8)	21	0	27.5	100
%HypoE >10 (n=3)	26	0	10.3	100

12.8 ± 0.9 g/dl at 6 months ($P < 0.0001$). The increases were always significant between the basal mean, the 2nd month, 4th month and 6th month (Table 2).

Iron status evolution (Table 2)

Serum ferritin levels increased from 137 µg/l baseline to 456 µg/l ($P = 0.0001$) at 6 months. Between the 4th and 6th month, the increment did not reach statistical significance and, therefore, a 'plateau' may have been reached by the 4th month. Serum iron remained stable between 65 and 70 µg/dl without any significant variation over the whole study period. Transferrin levels were decreased at the 2nd month ($P < 0.0001$) and remained stable thereafter. The percentage of transferrin saturation, after a significant initial rise, also stabilized. The percentage of hypochromic erythrocytes had a similar evolution; a decrease at the 2nd month with no significant change in the remaining period.

We did not find any correlation between serum ferritin and the percentage of transferrin saturation from the beginning to the end of the study. In the same way, no correlations were found between ferritin and the percentage of hypochromic erythrocytes.

Erythropoietin use

The utilization of rHuEpo decreased from 6871 units/patient/week to 4947 units/patient/week (28% change) at 6 months ($P < 0.003$). Consequently the dose/kg/week of 118 units decreased to 84, providing a significant economic benefit.

Target ferritin

In order to define a target value to maximize the use of i.v. iron, we compared patients with 'low initial

ferritin' (Group I, SF <100 µg/l) and 'high initial ferritin' (Group II, SF between 100 and 400 µg/l). Table 3 shows that final haemoglobin was not significantly different; on the contrary, mean ferritin levels continued to be significantly lower in group I throughout the whole study despite continuous supplementation of i.v. iron. Serum iron was identical in both groups at baseline but became significantly higher in group I beginning at month 2. Group I 'low ferritin' had higher basal transferrin levels and until the 4th month. The percentage of transferrin saturation was identical in both groups at baseline, but was higher in group I at the end of the study. The percentage of hypochromic erythrocytes was identical in both groups throughout the entire study. Group I required a lower dose of rHuEpo during the whole study and the difference almost reached statistical significance ($P < 0.07$) by the 6th month.

Previous use of oral iron

Twenty of the 33 treated patients had a prescription of oral iron. However, their mean ferritin values (130 ± 106 µg/l) did not differ significantly from those who were not on oral iron (147 ± 106 µg/l). Also the increases in haemoglobin and in ferritin were not different between patients with or without a prescription for oral iron before the study.

Suspension of i.v. iron

Twelve patients with ferritin >600 µg/l discontinued i.v. iron until serum ferritin levels declined to <400 µg/l. All of them were entirely free of any clinical or biochemical dysfunction attributable to iron overload.

Adverse reactions

Four patients complained of 'metallic taste', mainly when iron administration was too fast. There were no anaphylactic reactions, no skin rashes, and no signs of intestinal or respiratory allergy. We had no infectious complications throughout the study in patients on i.v. iron therapy. We did not observe any hepatic, pancreatic or cardiac dysfunction related to iron treatment.

Table 2. Effect of thrice-weekly low-dose i.v. iron for 6 months in 33 patients

	Baseline	2nd Month	P	4th Month	P	6th Month	P	P*
Haemoglobin (g/dl) ¹	10.8 ± 1.0	11.7 ± 1.1	0.0001	12.2 ± 1.1	0.0001	12.8 ± 0.9	0.0001	0.0001
Ferritin (µg/l) ²	137 ± 92	278 ± 138	0.0001	395 ± 221	0.0001	456 ± 169	NS	0.0001
Iron (µg/dl) ¹	65 ± 17	68 ± 19	NS	70 ± 19	NS	67 ± 19	NS	NS
Transferrin (mg/dl) ¹	193 ± 31	163 ± 26	0.0001	168 ± 30	NS	162 ± 26	NS	0.0001
%Sat. transferrin ¹	27 ± 8	34 ± 11	0.009	34 ± 11	NS	33 ± 10	NS	0.009
%HypoE ¹	5.6 ± 3.8	3.3 ± 2.3	0.0001	3.6 ± 2.5	NS	3.7 ± 3.0	NS	0.0001

*Comparison begin vs 6th month; ¹paired Student's *t* test; ²Wilcoxon signed rank test.

Table 3. Parameters of iron metabolism for patients with 'high' and 'low' ferritin levels

	Iron ¹ (µg/dl)		Transferrin ¹ (mg/dl)		%Sat. transferrin ¹		Ferritin ² (mg/l)		Haemoglobin ¹ (g/dl)		rHuEpo ² (u/kg/week)	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Group I												
Ferritin <100 (n=17)	66 ±26	79 ±26	211 ±45	169 ±37	25 ±10	38 ±13	49 ±26	383 ±201	10.9 ±1.1	13 ±1	112.3 ±73.3	73.4 ±48.0
Group II												
Ferritin >100 and <400 (n=16)	64 ±16 <i>P=n.s.</i>	56 ±19 <i>P=0.01</i>	174 ±27 <i>P=0.01</i>	153 ±25 <i>P=n.s.</i>	30 ±8 <i>P=n.s.</i>	29 ±9 <i>P=0.05</i>	230 ±74 <i>P=0.02</i>	533 ±198 <i>P=0.04</i>	10.6 ±1.6 <i>P=n.s.</i>	12.6 ±1.1 <i>P=n.s.</i>	124.5 ±62.8 <i>P=n.s.</i>	95.2 ±49.8 <i>P=0.07</i> <i>n.s.</i>

¹Non-paired *t* test; ²Mann-Whitney rank sum test.

Discussion

Routine treatment with i.v. iron

The mean increase of 2 g/dl in haemoglobin values after 6 months of i.v. iron is the best argument to favour the intravenous over the oral route. Oral iron, prescribed to patients with the lowest serum ferritin values, was not useful to replenish their organ stores of iron. On the contrary, patients who were not on oral iron had higher ferritin levels, although the difference did not reach statistical significance. Based on this evidence, we conclude that oral iron was not effective. Many nephrologists are aware that oral iron administration is not always sufficient because iron absorption can be abnormal in these patients [21]. However, routine i.v. administration of iron is not widely accepted because of concern about allergic side-effects and iron overload toxicity. We have no European data, but among United States haemodialysis patients receiving rHuEpo, the prevalence of iron deficiency is more than 50% [22]. In fact there are recent studies suggesting a decreased intestinal iron absorption in uraemic patients, even in those with iron deficiency [2,3], a finding not confirmed by others [4,5]. Additionally, a prospective controlled trial comparing i.v. iron, oral iron and placebo showed the inefficacy of oral iron in haemodialysis patients with a progressive decrease in iron deposits in the placebo group as well as in the group on oral iron therapy [8].

Utility of iron markers

Only eight of the 33 patients selected for treatment had transferrin saturation of less than 20%. Considering that 29 patients responded to i.v. iron, and consequently had some degree of iron deficiency, we conclude that the sensitivity of this criterion is low (27.5%) (Table 1). The percentage of hypochromic erythrocytes, with a sensitivity of 10.3%, was of no utility to treat these patients (only 3 of 29 responders would be treated). It is possible that these two criteria may be useful to identify iron-deficient patients with inflammatory diseases with retention of iron in the reticuloendothelial system and high serum ferritin

values [11,12,16,17]. Red-cell ferritin concentration has been used with some success in detecting iron deficiency [23], but its determination is time consuming and not readily available in the clinical laboratory. Recently reticulocyte haemoglobin content has been proposed as a highly sensitive marker of functional iron deficiency [24], but we have no experience with it. Both traditional and more sophisticated new methods to evaluate iron metabolism do not have an absolute sensitivity and specificity [25]. It is true that the specificity of these criteria (%TSAT and %HypoE) was very high, but if we really want to screen patients who would have some benefit from i.v. iron, we must use other more sensitive markers. It has been proved that the criterion serum ferritin <400 µg/l has a reasonable sensitivity/specificity (100/87.9%) relationship, and our results strongly recommend its use.

Target ferritin

This study corroborates others that suggest that the criterion of serum ferritin <100 µg/l is too restrictive and insensitive to guide iron supplementation [14,15]. The present study shows that a similar increase in haemoglobin with iron therapy is obtained in patients with serum ferritin between 100 and 400 µg/l and those with less than 100 µg/l. We found no significant adverse reactions to iron therapy in patients with serum ferritin below 600 µg/l. Higher values of serum ferritin were not studied at present and, therefore, no recommendations concerning the danger of iron overload can be made.

With the i.v. iron protocol we used in this study, group I patients needed less rHuEpo (73.4 units/kg/week) than those of group II (95.2 units/kg/week) to reach the same haemoglobin values. At baseline, group I had higher transferrin levels and later developed higher serum iron and percentage of transferrin saturation. The two groups behave differently in the way they metabolize iron. It appears that patients with low initial ferritin are more capable of utilizing iron, probably due to a genetic capability not present in the patients of group II. It would be interesting to look at the prevalence of haemo-

chromatosis alleles to determine whether there are differences between the two groups.

We cannot establish a 'normal' value for serum ferritin in haemodialysis patients. It seems probable that there is a wide range of individual variation and subpopulations with different behaviours regarding iron therapy and metabolism. However the goal of optimal replenishment of iron stores must be fulfilled to obtain the maximal benefit of rHuEpo with the minimal dose and side-effects. First we must exclude cases with iron overload or in which ferritin is not a good index of iron stores [16,17]. Then, 20 mg iron i.v. should be administered after each dialysis session and serum ferritin assessed on a monthly basis, trying to reach a stable 'plateau' of serum ferritin between 450 and 600 µg/l. Whenever serum ferritin reaches values over 600 µg/l, i.v. iron should be stopped, and restarted at half of the last dose once ferritin levels have decreased below 450 µg/l. This is the mean value at which the best balance between haemoglobin concentration, rHuEpo dosage and serum ferritin values is achieved.

Erythropoietin consumption

In the beginning of the study only two of 33 patients did not receive regular rHuEpo treatment. At the end, four patients had to discontinue rHuEpo and the mean consumption decreased from 118 to 84 units/kg/week. If the haemoglobin mean values at the end of the study (12.8 g/dl) were equal to the initial values of 10.8 g/dl, we would have saved much more rHuEpo.

Prevention of aluminium intoxication

Evidence indicates that haemodialysis patients with iron deficiency are at a higher risk of developing aluminium intoxication. One of the hypotheses to explain this susceptibility is that iron and aluminium share and compete for some of the same metabolic paths, e.g. intestinal absorption [26]. Recent studies [27] showed an inverse correlation between aluminium and iron serum levels and transferrin saturation respectively. Additionally this inverse correlation was greater in patients with higher serum iron and percentage of transferrin saturation. According to these authors, patients with higher iron deposits would have less positive DFO tests.

Conclusions

Routine supplementation of iron in haemodialysis patients should be performed intravenously. In a dialysis centre, 51.8% of patients proved to have a physiological iron deficiency when switched to i.v. iron therapy. This therapy resulted in a 28% decrease in rHuEpo consumption and a simultaneous increase in the average haemoglobin value from 10.8 to 12.8 g/dl (18.5%). If target haemoglobin was lowered, the rHuEpo dosage required would probably decrease even further.

Due to low sensitivity, the percentage of transferrin saturation and the percentage of hypochromic erythrocytes were not useful parameters to assess iron requirements of haemodialysis patients.

Patients with serum ferritin less than 100 µg/l had the same benefit in terms of haemoglobin increment as the ones with ferritin between 100 and 400 µg/l. No adverse effects of iron therapy were reported under values of 600 µg/l.

We recommend administration of 20 mg of i.v. iron, which is monitored by monthly ferritin levels aiming at a target between 450 and 600 µg/l and, afterwards, individualization of iron i.v. dose. The advantages of this protocol include more accurate iron administration and control, fewer rHuEpo side-effects, and cost, and possibly the prevention of aluminium intoxication.

We are aware that this is a single-centre study with a limited number of patients and should be confirmed by other multicentre prospective trials with larger numbers of patients.

References

1. Eschbach JW, Cook JD, Scribner BH, Finch CA. Iron balance in hemodialysis patients. *Ann Intern Med* 1977; 87: 710
2. Goch J, Birgegard G, Danielson BG, Wikstrom B. Iron absorption in patients with chronic uremia on maintenance hemodialysis and in healthy volunteers measured with a simple oral iron load test. *Nephron* 1996; 73(3): 403–406
3. Donelli SM, Posen GA, Ali MAM. Oral iron absorption in hemodialysis patients treated with erythropoietin. *Clin Invest Med* 1991; 14: 271–276
4. Macdougall IC. Poor response to erythropoietin: practical guidelines on investigation and management. *Nephrol Dial Transplant* 1995; 10: 607–614
5. Gokal R, Millard PR, Wheatherall DJ, Callender STE, Ledingham JGG, Oliver DO. Iron metabolism in haemodialysis patients. *Q J Med* 1979; 48: 369–391
6. Marchasin S, Wallerstein RO. The treatment of iron-deficiency anaemia with intravenous iron dextran. *Blood* 1961; 23: 354–358
7. Wingard RL, Parker RA, Ismail N, Hakim RA. Efficacy of oral iron therapy in patients receiving rHuEpo. *Am J Kidney Dis* 1995; 25: 433–439
8. Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE. A randomised controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 1996; 50(5): 1694–1699
9. Taylor JE, Peat N, Porter C, Morgan AG. Regular low-dose intravenous iron therapy improves response to erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 1996; 11(6): 1079–1083
10. Senger JM, Weiss RJ. Haematological and erythropoietin responses to iron dextran in the hemodialysis environment. *ANNA J* 1996; 23(3): 319–323
11. Macdougall IC, Cavill I, Hulme B *et al.* Detection of functional iron deficiency during erythropoietin treatment: a new approach. *Br Med J* 1992; 304: 225–226
12. Braun J, Lindner K, Schreiber M, Heidler RA, Hörl WH. Percentage of hypochromic red blood cells as predictor of erythropoietic and iron response after i.v. iron supplementation in maintenance haemodialysis patients. *Nephrol Dial Transplant* 1997; 12: 1173–1181
13. Van Wyck DB, Stivelman JC, Ruiz J, Kirlin LF, Katz MA, Ogden DA. Iron status in patients receiving erythropoietin for dialysis-associated anaemia. *Kidney Int* 1989; 35: 712–716
14. Allegra V, Mengozzi G, Vasile A. Iron deficiency in maintenance hemodialysis patients. Assessment of diagnosis criteria and of three different iron treatments. *Nephron* 1991; 57: 175–182

15. Eschbach JW. Turning points: anaemia. *Dial Transplant* 1996; 25: 725–727
16. Braun J, Hammerschmidt M, Schreiber M, Heidler R, Horl WH. Is zinc protoporphyrin an indicator of iron-deficient erythropoiesis in maintenance haemodialysis patients? *Nephrol Dial Transplant* 1996; 11(3): 492–497
17. Baldus M, Salopek S, Moller M *et al.* Experience with zinc protoporphyrin as a marker of endogenous iron availability in chronic haemodialysis patients. *Nephrol Dial Transplant* 1996; 11(3): 486–491
18. Sunder-Plassmann G, Horl WH. Erythropoietin and iron. *Clin Nephrol* 1997; 47(3): 141–157
19. Zanen AL, Adriaansen HJ, van-Bommel EF, Posthuma R, Th de Jong GM. 'Oversaturation' of transferrin after intravenous ferric gluconate (Ferrlecit(R)) in haemodialysis patients. *Nephrol Dial Transplant* 1996; 11(5): 820–824
20. Sunder Plassmann G, Hörl WH. Safety of intravenous injection of iron saccharate in haemodialysis patients. *Nephrol Dial Transplant* 1996; 11(9): 1797–1802
21. Valderrábano F. Erythropoietin in chronic renal failure. *Kidney Int* 1996; 50: 1373–1391
22. U.S. Renal Data Systems. The USRDS Dialysis Morbidity and Mortality Study (Wave 1) in National Institutes of Health, National Institute Diabetes and Digestive and Kidney Diseases. *U.S. Renal Data Systems 1996 Annual Data Report*. Ch. 4. Bethesda, MD, 1996; 45–67
23. Carvaca F, Vagace JM, Aparicio A *et al.* Assessment of iron status by erythrocyte ferritin in uremic patients with or without recombinant human erythropoietin therapy. *Am J Kidney Dis* 1992; 20: 249–254
24. Fishbane S, Galgano C, Langley RC Jr, Canfield W, Maesaka JK. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. *Kidney Int* 1997; 52: 217–222
25. Sunder-Plassmann G, Spitzauer S, Hörl WH. The dilemma of evaluating iron status in dialysis patients—limitations of available diagnostic procedures. *Nephrol Dial Transplant* 1997; 12: 1575–1580
26. Cannata JB. Aluminium toxicity. its relationship with bone and iron metabolism. *Nephrol Dial Transplant* 1996; 11 [Suppl 3]: 69–73
27. Cannata JB, Fernandez Martin JL, Diaz Lopez B *et al.* Influence of iron status in the response to the deferoxamine test. *J Am Soc Nephrol* 1996; 7(1): 135–139

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