www.bdd.rdplf.org Volume 2, n° 3, Septembre 2019
https://doi.org/10.25796/bdd.v2i3.20983
ISSN 2607-9917

Le Bulletin de la Dialyse à Domicile

What do we learn about the "Anemia Module" of the French language Peritoneal Dialysis ? Interest and Results.

(Que nous apprend le ''Module Anémie'' du Registre de dialyse Péritonéale de langue Française (RDPLF)? Intérêt et Résultats)

Note : this text is a translation of the original French article available at the same url : https://doi.org/10.25796/bdd.v2i3.20983

Belkacem Issad[1], Mireille Griuncelli[2], Christian Verger[3], et Guy Rostoker[2]

Services de Néphrologie du CHU Pitié/Salpêtrière[1], CHP Claude Galien–Quincy[2], Registre du RDPLF-Pontoise[3]

Résumé

Contexte : l'anémie est fréquente chez les patients insuffisants rénaux chroniques (IRC), dès que le débit de filtration glomérulaire devient inférieur à 30 ml/min. Les patients atteints d'IRC ont fréquemment un déficit en fer. C'est la raison pour laquelle une réserve en fer adaptée est essentielle pour atteindre le bénéfice thérapeutique optimal des agents stimulant l'érythropoïèse (ASE).
De nombreux groupes s'accordent à considérer que l'anémie des patients en dialyse péritonéale (DP) est moins importante que celle des sujets en hémodialyse (HD) et que les pratiques thérapeutiques pour la prise en charge de l'anémie diffèrent fortement entre DP et HD.
Méthodes : analyse du module Anémie du registre RDPLF au cours de la période 2010-2017.
Résultats : 568 patients ayant participé au module Anémie au cours de la période de suivi 2010-2017, ont été analysées. L'âge médian est de 71 ans, avec 42% de femmes, et la médiane de l'ancienneté en DP est de 13 mois, 40,5% sont diabétiques, 74% sont sous ASE, 23% sous fer oral et seulement 11% reçoivent du fer injectable. Sur le plan du bilan biologique, on constate qu'en moyenne le taux d'hémoglobine est proche de 12 g/dl et la médiane de la protéine C-réactive (CRP) est de 5 mg/l. Sur le plan du bilan martial, la ferritine après avoir atteint un taux moyen de 270 µg/l en 2013, s'est stabilisée à 200 µg/l en 2017. La saturation de la transferrine a toujours oscillé entre 23% et 25% de 2010 à 2017.
Conclusion: les résultats du module Anémie apparaissent en accord avec les valeurs cibles des recommandations européennes de l'ERA-EDTA (ERBP 2013) et mettent en évidence une faible utilisation de fer intraveineux en DP (en seconde intention).

Mots clés : anémie, dialyse péritonéale, fer intraveineux, ferritine, hémodialyse, RDPLF.

Abstract

Background: Anemia is commonly observed in patients with chronic kidney disease (CKD) as soon as the glomerular filtration rate falls below 30 ml/min. Iron deficiency is frequent. The use of both erythropoiesis-stimulating agents (ESA) and iron therapy is the backbone of anemia management in CKD. For this reason, an adequate iron supply is mandatory to achieve the optimal therapeutic benefit of ESAs. Many groups agree that anemia in peritoneal dialysis (PD) patients is less severe than in hemodialysis (HD) patients and that there are important differences in treatment practices for anemia between PD and HD patients.
Methods: Analysis of the Anemia module of the French Language Peritoneal Dialysis Registry (RDPLF) from the database during the period 2010-2017.
Results: Data from 568 patients who participated in the Anemia module were analysed during the 2010-2017 follow-up period. Their median age was 71 years, 42% were female, median dialysis vintage was 13 months, 40,5% of patients had diabetes mellitus, 74% were treated with ESA, 23% were on oral iron and only 11% have received intravenous iron. In terms of biological assessment, the average hemoglobin level was close to 12 g/dl and median CRP was close to 5 mg/l. As to iron balance, ferritin reached an average level of 270 µg/l in 2013 and stabilized in 2017 at 200 µg/l. The transferrin saturation coefficient always fluctuated between 23 % and 25 % from 2010 to year 2017.
Conclusion: The results of the Anemia module of the RDPLF registry appear to be in line with the target values of the ERA-EDTA latest European guidelines on anemia (ERBP 2013) and show the low use of intravenous iron in PD (usually as second line therapy).

Keywords : Anemia, ferritin, hemodialysis, intravenous iron, peritoneal dialysis, RDPLF.

journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 2, n° 3, Septembre 2019
https://doi.org/10.25796/bdd.v2i3.20983
ISSN 2607-9917

INTRODUCTION

The development of erythropoiesis-stimulating agents (ESA) has resulted in benefits for patients with chronic kidney disease (CKD) including: significant improvement in quality of life, reduced blood transfusions and HLA sensitization, decreased left ventricular mass, a decrease in sleep disorders, and an increase in physical capacity[1, 2]. Unfortunately, a considerable proportion of patients treated with ESA have a suboptimal hematologic response. A European survey on the management of dialysis anemia in 2003 showed that 66% of patients had a hemoglobin level of 11 g / dl or more, and only 48% had a suitable martial status defined by ferritin greater than 100 µg / ml, transferrin saturation greater than 20% or hypochromic red blood cells less than 10%[3]. These results suggested that adequate iron supplementation is required to provide patients with an appropriate hematologic response to ESAs. However, recent publications warn against excessive prescription of intravenous (IV) iron as sometimes practiced in France and Europe and more often in the United States[4-6]. These practices have led the National Agency of Safety of Medicines and Health Products (ANSM) to the publication of a newsletter for the attention of prescribers[7] and epidemiologists in the group Dialysis Outcomes and Practice Patterns Study (DOPPS) recently showed that there was a relationship between very high doses of IV iron (greater than 300 mg / month) and mortality in HD[8]. This excessive use of injectable iron in hemodialysis may also lead to hepatic iron overload, which has been demonstrated by the quantitative magnetic resonance imaging (MRI) method from 2011 onwards as shown in various publications both in France and abroad[9-11].

We present here exclusively the data of management and therapeutic practices of the Anemia module (Metropolitan France) from 2010 to 2017 among 568 patients treated with PD.

METHODS

We analyzed raw data from the French-language Peritoneal Dialysis Registry (RDPLF) from the Anemia module comprising 568 patients reported from 2010 to 2017. One of the hypotheses of this work was that martial supplementation practices differed significantly between HD and DP.

Data collection

Data on anemia were recorded in the database from 2005; analysis of anemia treatment prior to this date was performed on the main module, which was more exhaustive but less detailed and therefore sometimes on slightly different patient populations and centers. A total of 9,467 anemia assessments were performed in 358 patients in 17 centers in mainland France. On the one hand, we report the results of the Anemia module in 568 patients managed with PD during the period 2010-2017, during which time the therapeutic strategies evolved and / or the raw data of the Anemia module have been completed. On the other hand, we analyzed in detail the data of anemia management during the year 2017 where only the last examination was taken into account for each patient and we only retained the files for which we had full confirmation regarding the iron and ESA treatments.

Statistical analysis

Statistical analyzes of the RDPLF Anemia module data included a descriptive analysis of the different variables and the comparison of the different variables over the years by parametric or non-parametric analysis of variance for the quantitative variables.

RESULTS

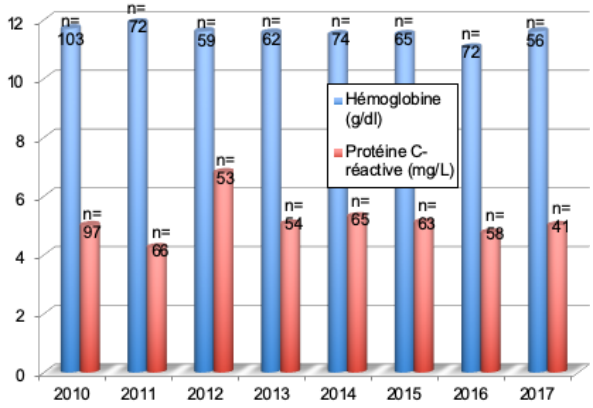

Figure 1 Evolution of hemoglobin and C-reactive protein from 2010 to 2017 in 568 patients treated with peritoneal dialysis (data from the RDPLF registry)

1 ° Analysis of the demographic data and therapeutic modalities of 568 patients from 2010-2017 in RDPLF Anemia module.

The demographic data are presented in Table I.

This table shows a significant proportion of diabetic patients (40.49%). The majority of these patients are treated with ESA (73.77%) and 34.15% receive iron

www.bdd.rdplf.org Volume 2, n° 3, Septembre 2019
https://doi.org/10.25796/bdd.v2i3.20983
ISSN 2607-9917

Table I: demographics and caracteristics of anemia management in 568 patients on PD from the RDPLF registry (2010-2017).
The values indicated are the median (with distribution interval), the percentage of patients (%) and the number of patients (n).

Variables	**Patients on PD (n= 568)**
Age (years)	71,2 (18,2 – 93,3)
females (%) (nF	42,43% (241/568)
Dialysis vintage (months)	13,57 (11,99 – 23,36)
Patients receiving ASE (%) (n)	73,77% (419/568)
Patients receivig iron (IV or oral) (%) (n)	34,15% (194/568)
Patients receiving intravenous iron (%) (n)	11,27% (64/568)
Patients receiving oral iron (%) (n)	22,89% (130/568)
Diabetic patients (%) (n)	40,49% (230/568)

treatment (oral or intravenous). However, only 11.27% of patients receive injectable iron.

Biological markers of the martial stock (2010-2017)

Biomarker data are presented in Table II as a whole.

These rates do not differ significantly in the Kruskal-Wallis non-parametric variance analysis test (Table III).

Evolution of ferritin and rate of transferrin saturation

Data on ferritin and transferrin saturation are presented globally by year in Figure 2.

Table II: Median values of biological markers of iron stock from 2010 to 2017 in 568 patients treated with peritoneal dialysis (data from the RDPLF register).

The values indicated are the median (with distribution interval).

Variables	Patients on PD (n= 568)
Hemoglobin (g/dL)	11,6 (7,2-19,9)
Serum ferritin (μg/L)	209,4 (10-1565)
Serum iron (μmol/L) or μg/100ml	12,43 (4-42,2)
Serum transferrin (g/L)	2,04 (1,02-3,7)
Transferrine saturation coefficient (TSAT) (%)	24 (6,6-93)
C-réactive protein (mg/L)	5 (0,2-283)

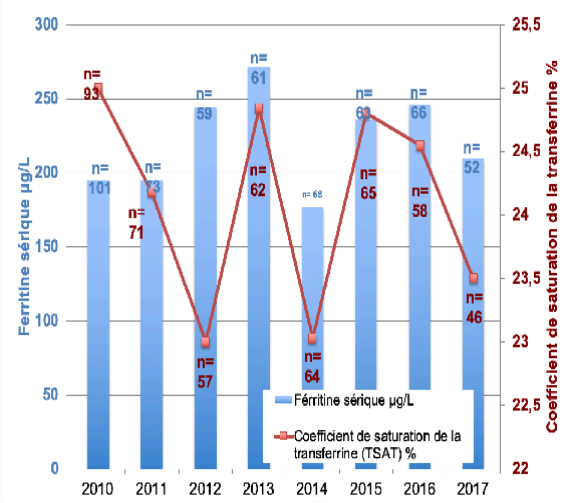

Figure 2: Evolution of ferritin and transferrin saturation coefficient from 2010 to 2017 in 568 PD-treated patients (RDPLF data)

Table III: Annual comparison of biomarkers in 568 DP-treated patients (RDPLF data).

The values given are the median (with distribution interval) and the significance test of Kruskal-Wallis (p).

Variables	2010	2011	2012	2013	2014	2015	2016	2017	kruskal-Wallis test (P)
Hemoglobin (g/dL)	11,7 (7,2-15,7)	11,9 (8,9-14,7)	11,7 (7,2-15,7)	11,6 (7,3-15,1)	11,5 (7,8-14,2)	11,5 (8,7-14,3)	11,05 (7,7-15,7)	11,6 (9,1-14,0)	P= 0,0583
Serum ferritin (μg/L)	195,0 (12-993)	195,0 (23-1306)	244,0 (29-1557)	272,0 (16-1180)	176,5 (52-913,3)	236,0 (29-1280)	246,0 (10-1276)	209,2 (26-1565)	P= 0,3814
Transferrin saturation coefficient (TSAT) (%)	25 (10,3-93)	24,18 (7,2-68,6)	23 (10,4-62)	24,84 (6,6-53,8)	23,03 (11,6-84)	24,8 (7,8-52,8)	24,55 (9,8-68)	23,5 (8,9-86,1)	P= 0,9263
C-réactive protein (mg/L)	5 (0,6-107)	4,25 (0,3-69,6)	6,8 (0,2-163)	5,05 (1-109)	5,3 (1-283)	5,1 (0,6-253)	4,75 (0,6-87,6)	5 (0,7-139)	P= 0,3068

www.bdd.rdplf.org Volume 2, n° 3, Septembre 2019
https://doi.org/10.25796/bdd.v2i3.20983
ISSN 2607-9917

Ferritin, after reaching an average level of 270 µg/ l in 2013, gradually stabilized at around 200 µg/ l. The transferrin saturation coefficient varies between 23 and 25% between 2010 and 2017. The variations of the levels observed during this period for ferritin and the transferrin saturation coefficient do not appear clinically and statistically significant. The median serum ferritin level reached 195 µg/ l in 2010 to stabilize at 209 µg/ l in 2017 with a peak at 272 µg/ l in 2013 (P = 0.3814 in the Kruskal-Wallis test). The median transferrin saturation coefficient is 25% in 2010 and 23.5% in 2017, a remarkably stable value over time (P = 0.9263 on the Kruskal-Wallis test) (Table III).

Therapeutic modalities

In 194 patients undergoing martial treatment, intravenous iron doses range from 50 mg to 1000 mg / month (64 patients) and oral iron doses from 33 mg to 1056 mg / month (130 patients) depending on the products used.

2 ° Detailed analysis of the management of anemia during the year 2017

The overall hemoglobin distribution of PD patients in 2017 (293 patients in 28 centers) is shown in Figure 3. Patients without and under ESA were included. This figure shows that 16% of patients have a hemoglobin level greater than 13 g / dl.

The distribution of the hemoglobin level of the PD patients only treated with ESA in 2017 is given in Figure 4.

It is noted that 11.9% of patients have a hemoglobin level greater than 13 g / dl.

Treatment data for iron anemia and ESA in 293 patients are listed in Figure 5.

This shows that 33.1% of patients on PD receive neither ESAs nor iron. The rate of administration of ESAs according to the product used is given in Figure 6.

Table IV: Number of Patients on ESA, Oral Iron and IV Iron in 568 Patients on PD (RDPLF Registry Data)

	Receiving ESA	Receving oral iron	Receiving IV iron
Number of patients, n (percentage (%))	419 (73,8 %)	130 (22,9%)	64 (11,3%)

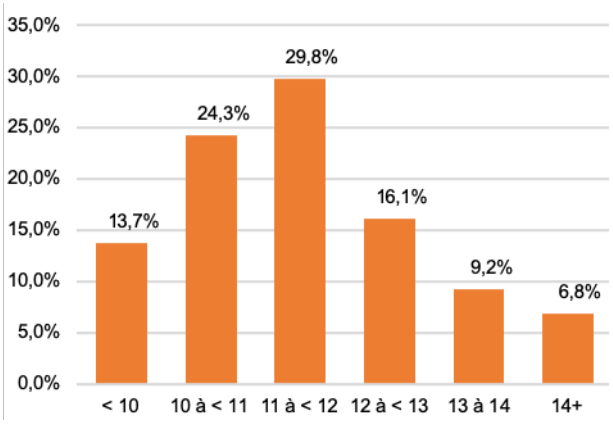

Figure 3: Hemoglobin distribution of patients on PD in 2017 (RDPLF registry data).

All patients included (with and without ESA.)

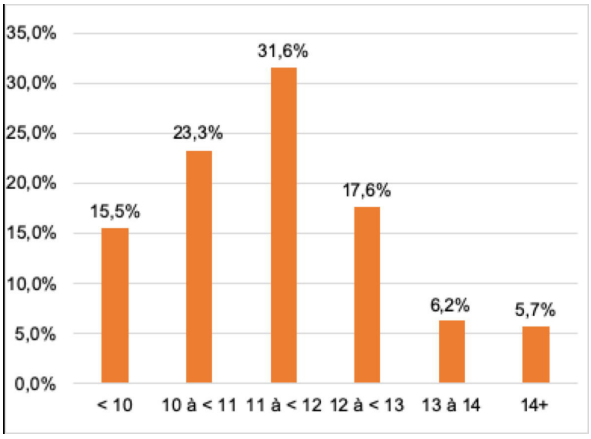

Figure 4: Distribution of hemoglobin levels in patients treated with ESA and DP in 2017 (RDPLF data).

Only patients receiving an ESA are included

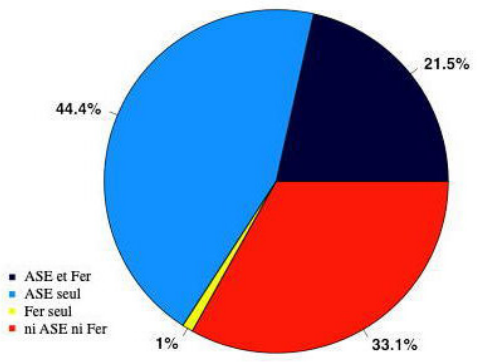

Figure 5: Anemia treatment with Iron and ASE of PD Patients in 2017 (RDPLF Registry Data)

www.bdd.rdplf.org Volume 2, n° 3, Septembre 2019
https://doi.org/10.25796/bdd.v2i3.20983
ISSN 2607-9917

It is observed that in 83.7% of patients on Epoetin-beta-pegol, the frequency was one injection every 5 weeks.

DISCUSSION

Patients with chronic kidney disease frequently have iron deficiency, which is why an adequate stock is essential for maximum benefit of ESAs. Decreasing iron stores or decreasing iron availability are the most well-known reasons for resistance to ESAs [12]. However, several authors agree that the consumption of iron is less important in PD than in HD, and this for several reasons [13, 14]. It is noted that blood losses differ between PD and HD [15]. Loss of iron in PD is much less important than in HD. By contrast, HD digestive losses are much higher following anticoagulation with heparin or low molecular weight heparins (LMWH) of extracorporeal circuits (Table V).

This contrast between HD and PD partly explains the more frequent use of iron and ESAs in HD, especially since true iron deficiency cannot be compensated by a sufficient absorption of iron in the gastrointestinal tract (related to iron chelation by various drugs and hyper-hepcidinemia observed in terminal IRC) [16]. We also note that the recommendations of good practices (KDIGO 2012, ERBP 2013) [17, 18] strongly differ between HD and PD. Indeed, is used almost constantly in first line in HD whereas it is an option in PD and IV iron doses are less important in PD than in HD. Prior to the ESAs era, secondary dialysis hemosiderosis

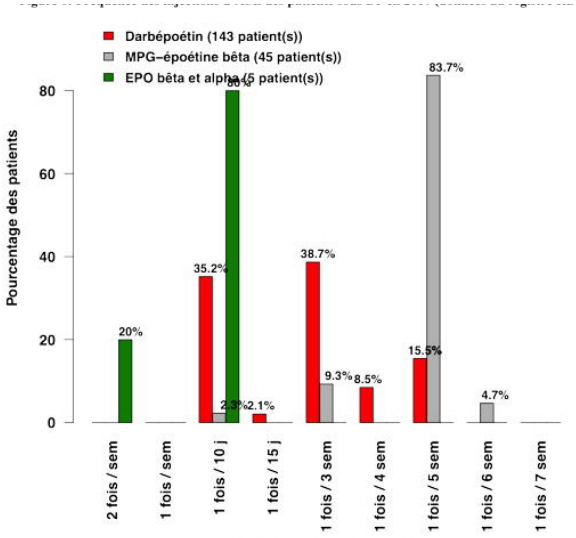

Figure 6: Frequency of ESA Injection of PD Patients in 2017 (RDPLF Registry Data)

Table V: Iron losses and management of iron deficiency in peritoneal dialysis and hemodialysis (according to Rottembourg J and Rostoker G. Nephrol Therap., 2015; 11 (7): 531-542) [15]

	Peritoneal Dialysis	Hemodialysis
Iron loss	- Digestive losse idem chronic renal desease 3,15 ml/day soit 1130 ml/year - Secondary loss due to biological samples : 428 ml/year - total blood loss : 1,5 l/tear (750 mg of iron)	- iron loss in hemodialysis patients (dialysers + circuits) : 165 ml of blood/ year (82,5 mg of iron/year) - Digestive loss (micro-bleeding) : 2257 ml of blood/year (1129 mg of iron /year) - Biological samples for folow up of uremic state : 428 ml of blood/year (214 mg of iron /year) - total blood loss of patients with fistula : 2,6 l of blood /year (1340 mg of iron /year) - total blood loss of patients with permanent cathter : 5,3 l of blood / year (2765 mg of iron / yaer)
Ferritin target	> 100 µg/l (KDIGO 2012, ERBP 2013)	250 µg/L – 500 µg/L KDIGO 2012 100 µg/L – 300 µg/L ERBP 2013
Use of IV iron products	Scarce 2ième or 3ième line of iron therapy (oral iron intolerance) or sever iron deficiency	Almost constant 1ière line therapy

was well known by nephrologists, linked, inter alia, to transfusions. However, studies conducted in the 1980s prior to the discovery of ESAs showed on autopsy data that there was a clear link between tissue iron overload, multiple transfusions, and IV iron infusions [19]. The Canavese study in 2004 [20] in 40 hemodialysis patients analyzed by the susceptometry method (SQUID) showed that 32% of patients had mild overload and 37% had severe overload. Rostoker et al. published in 2012 in the American Journal of Medicine a prospective observational study in 119 hemodialysis patients [21]. In this study, the hepatic iron overload, under IV martial treatment conducted according to the KDOQI and ERBP standards in force, was evaluated by quantitative magnetic resonance imaging (MRI) analysis of the hepatic iron stock according to the method of the University of Rennes. These patients were treated with darbepoetin alfa and IV iron sucrose. Of the 119 patients, only 19 had a normal liver iron stock. Nearly 30% of patients had severe iron overload (> 200 µmol / g dry liver, as observed in genetic hemochromatosis). Ferritin level (approximately 440 µg / ml) in patients

https://doi.org/10.25796/bdd.v2i3.20983
ISSN 2607-9917

with significant overload in quantitative MRI was, however, within the targets recommended by nephrology societies. There was a correlation between hepatic iron overload and the cumulative dose and the monthly dose of iron administered. However, no study was concerned with the assessment of iron overload on PD. Due to the very different therapeutic modalities between HD and PD, PD represents a true model for martial metabolism study in the terminal renal chronic disease, almost independently of the IV iron administration which is rarely used. The results of a recently published study on the hepatic martial stock, carried out in France in 32 patients treated by PD, show that the martial stock of the body appears most often normal in patients on PD [22]. In fact, quantitative liver MRI revealed in this study a normal iron stock in 81.3% of PD patients, compared to 16% in a first cohort of French patients on HD and 35% in a second cohort of HD patients. The mirror appearance of hepatic iron concentrations thus clearly appears between DP and HD. These data suggest that the ferritin targets proposed by the PD standards are quasi-physiological (ferritin> 100 µg / ml) and supra-physiological in HD (ferritin target between 250 and 500 µg / ml).

CONCLUSION

The data analysis of the Anemia module of the RDPLF registry makes it possible to evaluate the possible differences in practice with respect to the 2013 ERBP reference. Our study shows that the French nephrology teams most often have results within the proposed targets by the European standard for both hemoglobin and martial status. This work also confirms the interest of this module in approaching the reality of the management of anemia as well as its potential for future epidemiological studies for the evaluation of new stabilizing therapies of hypoxia-inducible factor (HIF). -Stabilizers), subject to the completeness of the transmission of information by the teams practicing PD. However, given the number of patients and centers, the figures presented should be interpreted with caution. Nevertheless, they represent the practices of the centers most concerned by this aspect of the management of PD patients.

DISCLOSURE

The authors declare that they have no conflict of interest for this articl

REFERENCES

[1] Valderrábano F. Erythropoietin in chronic renal failure. Kidney Int. 1996 Oct; 50(4):1373-91.

[2] Benz RL, Pressman MR, Hovich ET, Peterson DD. A preliminary study of the effects of correction of anemia with recombinant human erythropoietin therapy on sleep, sleep disorders, and daytime sleepiness in hemodialysis patients (The SLEEPO Study). Am J Kidney Dis. 1999 Dec; 34(6):1089-95.

[3] Jacobs C, Frei D, Perkins AC. Results of the European Survey on Anaemia Management 2003 (ESAM 2003): current status of anaemia management in dialysis patients, factors affecting epoietin dosage and changes in anaemia management over the last 5 years. Nephrol Dial transplant. 2005 May;20 Suppl 3:iii3-24.

[4] Rostoker G, Vaziri ND, Fishbane S. Iatrogenic iron overload in dialysis patients at the beginning of the 21st century. Drugs. 2016 May;76(7):741-57.

[5] Vaziri ND. Epidemic of iron overload in dialysis population caused by intravenous iron products: a plea for moderation. Am J Med. 2012 Oct;125(10):951-2.

[6] Freburger JK, Ng LJ, Bradbury BD, Kshirsagar AV, Brookhart MA. Changing patterns of Anemia Management in US hemodialysis patients. Am J Med. 2012 Sept;125(9):906-14.e9.

[7] Traitement de l'anémie des hémodialysés par solutions de fer IV : l'ANSM rappelle la nécessité de respecter les schémas posologiques de l'AMM - Point d'information 18/02/2013. Consulté sur https://ansm.sante.fr/

[8] Baillie GR, Larkina M, Goodkin DA, et al. Variation in intravenous iron use internationally and over time : the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2013 Oct;28(10):2570-9.

[9] Cecchin E, De Marchi S, Querin F, Marin MG, Fiorentino R, Tesio F. Efficacy of hepatic computed tomography to detect iron overload in chronic hemodialysis. Kidney Int. 1990 Mar;37(3):943-50.

[10] Rostoker G, Laroudie M, Blanc R, et al. Signal-intensity-ratio MRI accurately estimates hepatic iron load in hemodialysis patients. Heliyon. 2017 Jan 5;3(1): e00226.

[11] Gandon Y, Olivié D, Guyader D, et al. Non-invasive assessment of hepatic iron stores by MRI. Lancet. 2004 Jan 31;363(9406):357-62.

[12] Celi J, Samii K, Perrier A, Reny JL. Anémie ferriprive, inflammatoire ou mixte : comment orienter le diagnostic ? Revue Médicale Suisse. 2011 Oct 19;7(13):2018-2023.

[13] Richardson D, Bartlett C, Jolly H, Will EJ. Intrave-

https://doi.org/10.25796/bdd.v2i3.20983
ISSN 2607-9917

nous iron for CAPD populations: proactive or reactive strategies? Nephrol Dial Transplant. 2001 Jan;16(1):115-9.

[14] Vychytil A, Haag-Weber M. Iron status and iron supplementation in peritoneal dialysis patients. Kidney Int Suppl. 1999 Mar;69:S71-8.

[15] Rottembourg J, Rostoker G. Utilisation des dérivés injectables du fer au cours de la maladie rénale chronique : intérêts, limites et conseils pour un bon usage. Nephrol Ther. 2015 Dec;11(7):531-42.

[16] Fievet P, Brazier F. Fer, hepcidine et insuffisance rénale chronique. Nephrol Ther. 2011 Apr;7(2): 86-91.

[17] Magdougall IC, Bircher AJ, Eckardt KU et al. Iron management in chronic kidney disease: conclusions from a "kidney disease: improving global outcomes" (KDIGO) controversies conference. Kidney Int. 2016 Jan;89(1):28-39.

[18] Locatelli F, Bárány P, Covic A, et al, on behalf of the ERA-EDTA ERBP Advisory Board. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant. 2013 Jun;28(6):1346-59.

[19] Ghoti H, Rachmilewitz EA, Simon-Lopez R, et al. Evidence for tissue iron overload in long-term hemodialysis patients and the impact of withdrawing parenteral iron. Eur J Heamatol. 2012 Jul;89(1):87-93.

[20] Canavese C, Bergamo D, Ciccone G, et al. Validation of serum ferritin values by magnetic susceptometry in predicting iron overload in dialysis patients. Kidney Int. 2004 Mar;65(3):1091-8.

[21] Rostoker G, Griuncelli M, Loridon C, et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. Am J Med. 2012 Oct;125(10): 991-999.

[22] Issad B, Ghali N, Beaudreuil S, Griuncelli M, Cohen Y, Rostoker G. Hepatic iron load at magnetic resonance imaging is normal in most patients receiving peritoneal dialysis. Kidney Int Rep. 2017 Jul 23;2(6):1219-1222.

Received 2019/08/06, accepted after revision 2019/09/06, published on 2019/09/20