Anaemia Management in Non-Dialysis Chronic Kidney Disease: Flexibility of Target to Target Stability?

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Key Words

Anaemia · Epoetin · Chronic kidney disease · Haemoglobin variability · End-stage renal disease

Abstract

International clinical practice guidelines have recently recognized for the first time the concrete difficulty of keeping chronic kidney disease (CKD) patients within the narrow haemoglobin (Hb) target recommended of 11–12 g/dl (110–120 g/l) because of the variability of individual patient Hb levels. This emerging clinical problem has been the topic of several editorials that, however, exclusively focused on haemodialysis patients. Recently, 3 retrospective studies have been published on Hb variability in non-dialysis CKD. The studies which overall included more than 6,000 patients showed that Hb variability in non-dialysis CKD is greatly prevalent and is associated with a worse cardiorenal outcome. This minireview summarizes the results and limits of these studies and discusses the potential implications for clinical practice.

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KDOQI recommendations on haemoglobin (Hb) target [2] updated in September 2007 because of the new evidence of the potential harm deriving from therapy with erythropoiesis-stimulating agents (ESA) aimed at complete normalization of Hb levels [3]. Interestingly, both documents recognize, for the first time, the concrete difficulty of keeping patients within the narrow Hb target window recommended of 11–12 g/dl (110–120 g/l) because of the inpatient Hb variability (or cycling of individual patient Hb levels). This phenomenon, defined as the degree by which repetitive measures of Hb vary in the same subject over time, cannot be attributed to laboratory flaws because of the relatively low coefficient of variation in Hb testing [4, 5], and it is distinct from the expected interindividual variability.

Hb variability has recently emerged as hot topic in nephrology. Various editorials have analyzed the large body of data on Hb fluctuations, but exclusively in the haemodialysis (HD) setting, including the most recent one by Kalantar-Zadeh and Aronoff [6].

Hb Variability in Non-Dialysis Chronic Kidney Disease

Only a few studies have evaluated Hb variability in non-dialysis chronic kidney disease (ND-CKD) patients [7–9]. This is in stark contrast with the observation that

The Anaemia Working Group of the European Renal Best Practice (ERBP) has recently published a position statement on management of renal anaemia [1]. This document extends to European nephrologists the last

the size of the anaemic patient population is at least 10-fold greater in ND-CKD versus HD [10, 11]. Interestingly, in a multicentric survey of ND-CKD patients regularly followed in 26 Italian renal clinics, 52% of ESA-treated patients had Hb values <11 g/dl (110 g/l) with standard deviations of Hb ranging from 1.5 to 1.8 g/dl (15–18 g/l) from CKD stage 3–5 [12]. These findings, which resemble the discrepancy between ESA treatment and Hb outcome previously observed in HD [13, 14], suggest inadequate ESA therapy and high degrees of interpatient Hb variability in ND-CKD. To specifically address inpatient Hb variability, we recently reviewed the clinical data obtained from 1,198 visits during the first year of ESA treatment in 137 ND-CKD patients [9]. Varying Hb was found in 85.3% with downward changes in most cases (table 1). These figures have been confirmed by Boudville et al. [8] in a multicentre study of 6,165 ND-CKD patients, where Hb variability was detected in 73% of patients undergoing maintenance ESA therapy.

Interestingly, in normal subjects the individual variation of Hb levels occurs within the range of normal values and generally does not exceed 1 g/dl (10 g/l) [15, 16]. Maintenance of steady Hb levels is indeed mandatory to ensure consistent and adequate oxygen delivery to tissues. Conversely, with Hb cycling, oxygen delivered to tissues may fluctuate, leading to repeated episodes of relative ischaemia that could finally result in organ dysfunction or injury [6].

The detrimental effects of Hb fluctuations below the normal range may therefore become critical in conditions characterized by chronic hypoxia. In this regard, it is interesting to note that the constant maintenance of Hb levels above 11 g/dl (110 g/l) is already recommended by cardiologists in patients experiencing myocardial infarction and in those with heart failure [17, 18]. Similar recommendations probably apply to CKD. The majority of adults with moderate CKD, in fact, have coronary heart disease or risk equivalents and a high incidence of ischaemic cardiovascular events [12, 19–21]. While these observations support the need of Hb values steadily between 11 and 12 g/dl (110 and 120 g/l) to improve patient survival, it is possible to hypothesize benefits of stability of target Hb levels also in terms of nephroprotection. Indeed, recent studies have recently re-emphasized the role of chronic hypoxia in the tubulointerstitium as a final common pathway to end-stage renal disease (ESRD) [22, 23]. Specifically, the rarefaction of peritubular capillaries, typical in CKD, impairs oxygen diffusion and supply to tubular and interstitial cells leading to apoptosis or epithelial-mesenchymal

Table 1. Distribution of 137 ND-CKD patients according to the pattern of individual Hb variability during the 1st year of ESA therapy (modified from [9])

Hb, g/dl ¹	Prevalence, %
Constantly at 11–13	9.5
Constantly >13	0.7
Constantly <11	4.4
Fluctuating from 11–13 to <11	48.9
Fluctuating from 11–13 to >13	16.0
Fluctuating from <11 to >13	20.4

¹ To convert into SI units (g/l), multiply by 10.

transdifferentiation; this in turn exacerbates fibrosis and chronic hypoxia, setting a vicious cycle whose end point is ESRD. In this picture, ensuring a stable correction of renal anaemia that is a main factor hindering oxygen delivery may contribute to retarding progression of renal fibrosis.

Such a theoretical background is supported by the outcome analyses of the studies on Hb variability in ND-CKD. Boudville et al. [8] evidenced in their large cohort of ND-CKD patients a 30% increment in the risk of death per 1 g/dl (10 g/l) of residual standard deviation of Hb, which is a recognized measure of Hb variability [6]. When patients were divided into categories of Hb variability, with the reference group constituted by patients with Hb constantly at 11–13 g/dl (110–130 g/l), the greatest association with mortality was found for the subgroup of patients with Hb steadily below 11 g/dl (110 g/l) and for patients with Hb fluctuating from 11–13 g/dl (110–130 g/l) to below 11 g/dl (110 g/l). Conversely, no significant increase in mortality risk was found for patients with Hb steadily above 13 g/dl (130 g/l). The association between Hb variability and mortality was still significant even after adjustment for absolute Hb values and Hb trend (intercept and slope, respectively). Similarly, we found in our cohort that the risk of renal death (death or ESRD) was 58% lower in patients who spent almost the entire 1st year of ESA therapy with an Hb ≥ 11 g/dl (110 g/l) with respect to those who maintained these levels for only 3 months [7]. Nonetheless, it is important to underline that, as in the case of the HD setting [6], the available data on Hb cycling and outcomes in ND-CKD, being all associative and having been obtained in retrospective analyses, cannot prove causal relationship.

Therapeutic Perspectives

While identification of therapeutic strategies aimed at limiting Hb variability certainly needs to be explored by interventional studies, knowledge of the potential determining factors in daily practice represents a first critical step. In HD patients, proposed determinants of Hb variability are multiple and often hardly modifiable, such as cycling variation of fluid status, pre-existing co-morbid conditions, acute intercurrent infections and chronic inflammation [6, 24]. In this setting, patient characteristics account for very little Hb variability, as suggested by the very low R^2 of the regression model (0.019) used by Yang et al. [25] to identify potential predictors of increased Hb variability in a large HD population.

This may change in the non-dialysis setting where the burden of unmodifiable factors is less evident. Indeed, Boudville et al. [8] found that use of ESA, younger age, variability of glomerular filtration rate and lower albumin levels were all predictors of Hb variability with an R^2 of the regression model of 0.113; this value is definitely greater than that reported above for HD patients but it is still low, meaning that factors other than those considered accounted for the major part of the Hb variability [8].

More insights into the potential determinants of this phenomenon were provided in the 2 studies by our group. In our ND-CKD cohort, basal glomerular filtration rate and Hb levels at the beginning of ESA therapy were directly and independently associated with the length of time spent with Hb at target (time in target) in the subsequent year of treatment [7]. These data suggest that positive effects on Hb stability may be attributed to the timely intervention with ESA. It is reasonable to hypothesize that the earlier ESA therapy is started, the higher are the levels of endogenous epoetin, which may contribute to ensuring steadiness of Hb target levels during exogenous ESA administration. Interestingly, a similar correlation with time in target was also found for first epoetin dose and iron supplementation. Overall, these observations suggest a main role for therapeutic intervention. In fact, inadequate epoetin levels, either endogenous or exogenous, are associated with shorter survival of red cells, while a lack of iron can lead to haematopoietic deficiencies [26–28]. Interestingly, the 2 phenomena may also be interrelated. Recent studies have in fact evidenced that serum levels of hepcidin, an inhibitor of iron release from reticulo-endothelial cells and of iron uptake in the gut, are elevated in ND-CKD [29]; more importantly, increased hepcidin, be-

sides contributing to abnormal iron regulation, might also directly inhibit erythroid progenitor proliferation and survival when epoetin levels are low [30]. Therefore, it is possible to hypothesize that low levels of circulating epoetin may activate adverse mechanisms such as neocytolysis and hepcidin transcription leading to a deficient haematopoietic response to ESA that interferes with Hb stability. Indeed, in our study, the first mean ESA doses were in the low range, that is 25 $\mu\text{g}/\text{week}$ for darbepoetin and 4,500 IU/week for epoetin [7]. More importantly, nephrologists generally did not uptitrate doses in the subsequent control visits even when they recognized that the Hb goal had not been met. This ‘conservative’ attitude may extend to other renal clinics in the multicentric survey in Italy described above [12]. In fact, the median ESA dose during the maintenance phase of ESA therapy was 23 $\mu\text{g}/\text{week}$ for darbepoetin and 4,000 IU/week for epoetin.

Therapeutic inertia in the use of ESA, i.e. the provider's failure to modify the ESA dose despite recognition that treatment goals are unmet, therefore, emerges as a potential determinant of Hb cycling in ND-CKD. This hypothesis was supported in our most recent study, showing that a change of ESA dose occurred in only half of control visits where it was expected on the basis of guidelines' recommendations, and that higher degrees of therapeutic inertia were associated with greater Hb variability, characterized by downward fluctuations in most cases as well as the risk of renal death [9]. This study also confirmed the role of the first ESA dose. Indeed, only a minority of patients responded adequately to the first ‘low’ dose with an increase in the Hb level from about 10 to ≥ 11 g/dl within the first 2 months and maintenance of target levels thereafter. Conversely, most patients hardly achieved and maintained the Hb target despite similar ESA dosing. Indeed, physicians did not increase the ESA dose in all patients, that is in patients who showed greater responsiveness to ESA, those who required any or only minor changes of ESA dosages and in ‘low responder’ patients who, conversely, required an increment of the ESA dose. In the latter group, the reduction of endogenous epoetin levels below erythropoietic threshold and the ensuing activation of hepcidin pathway and neocytolysis may have contributed to the greater rate of downward Hb fluctuations.

The different Hb responsiveness to ESA could not be ascribed to the so-called ESA resistance because no difference was found in the prevalence of the main causes of this phenomenon (co-morbidities, iron deficiency, hyperparathyroidism, impaired nutrition, inflammatory

status, and administration of renin-angiotensin system inhibitors). Therefore, it is possible to hypothesize that the response to ESA was, at least in part, of biologic nature and independent of the recognized factors of ESA resistance.

The observational findings available at this moment on the determinants of Hb variability do not allow the definition of interventions specifically aimed at improving Hb stability; however, these data do actually reinforce the guidelines' recommendations on management of renal anaemia [1, 2]. Best treatment in terms of a timely start of ESA therapy, iron supplementation and 'active' monitoring of patients may in fact not only allow the achievement of Hb target levels but also permit a greater steadiness of these levels during the maintenance phase of ESA therapy (table 2). Nowadays, however, scarce implementation of the guidelines in nephrology is unfortunately frequent and multifaceted [12, 31]. In the specific case of anaemia treatment in ND-CKD patients, it is possible to hypothesize that physicians, being overwhelmed by the multiple interventions required in these patients, often feel more confident in giving a fixed low dose of ESA, even if not 'fully' efficacious. This position is probably further strengthened by the narrow target range now recommended, the concerns about Hb overshooting, as well as by the recognition of the potential negative effects of the use of ESA at a high dose (>10,000 IU/week) [32].

Conclusions

In ND-CKD, Hb variability is greatly prevalent and associated with worse cardiorenal outcome. However, the data so far collected are limited and of an observational nature. Further investigation is therefore needed prior to drawing any firm conclusion. Nevertheless, ob-

Table 2. Potential interventions to improve Hb stability in ND-CKD

Regular monitoring of renal function, Hb and iron status
Correct the main modifiable factors affecting erythropoiesis (hyperparathyroidism, impaired nutrition, inflammatory status)
Start ESA when Hb <11 g/dl (110 g/l) in 2 consecutive controls
Iron supplementation when ferritin <100 ng/ml or transferrin saturation <20%
Target therapy to Hb 11–12 g/dl (110–120 g/l) while accepting higher Hb levels for a limited period of time
Change ESA dose on the basis of Hb response also in the absence of recognized factors of ESA resistance

servational data are hypothesis-generating and essential to design prospective interventional studies that take into account Hb variability. In this regard, it is intriguing to hypothesize that this phenomenon may explain, at least in part, the contradictory results in the relationship between anaemia correction and patient outcome reported in the most recent randomized trials in ND-CKD [3, 33].

While awaiting more studies on Hb variability, nephrologists should follow the latest recommendation of the ERBP and KDOQI on the need of maintaining flexibility in the medical decision [1, 2]. As recently emphasized, in fact, clinical guidelines are supposed to be guides, not rules, and tailoring of therapy is a critical aspect of management because 'one size certainly does not fit all patients' [34]. This concept may be particularly important for the optimal management of CKD-related anaemia because flexibility is likely essential to obtain adequate steadiness of target Hb levels.

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Editorial Comment

M. El Nahas, Sheffield

The minireview by De Nicola et al. focuses on the importance of haemoglobin (Hb) variability in pre-dialysis chronic kidney disease (CKD) patients. It re-emphasizes the growing concern relating to Hb variability and subsequent morbidity and mortality. Up to very recently, attention in the management of anaemia in CKD and end-stage renal disease (ESRD) has focused almost exclusively on target Hb levels. But more recent attention has highlighted the issue of Hb fluctuations. Cohort studies suggest that Hb fluctuations may be associated with worse cardiovascular outcomes. Whether this is directly related to the Hb fluctuations per se or the underlying comorbidities that lead to these fluctuations is difficult to untangle. From past experience, cohort studies in nephrology, including those in the field of anaemia man-

agement, were not supported by prospective randomized clinical trials such as CHOIR and CREATE! However, there is little doubt that Hb fluctuations outside the target range occur frequently in CKD/ESRD patients [1]. Nephrologists need to pay more attention to these fluctuations and optimize their therapeutic response to maintain patients within the target range and minimize wide fluctuations.

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