

## Inflammation and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness

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### Abstract

The availability of erythropoiesis-stimulating agents (ESAs) has revolutionized the treatment of anaemia in patients with chronic kidney disease. However, maintaining patients at haemoglobin (Hb) levels that are both safe and provide maximal benefit is a continuing challenge in the field. Based on emerging data on the potential risks of Hb treatment targets > 13 g/dL, treatment targets have recently been lowered. In the latest revision (March 2008) of the European product labelling for the ESA class of drugs, the target treatment range was lowered to 10–12 g/dL. Fluctuation of Hb levels or ‘Hb variability’ during treatment with ESAs is a well-documented phenomenon. Hb levels that are either too high or too low may have an adverse effect on patient outcomes; thus, it is important to understand the causes of Hb variability in order to achieve optimal treatment. Several factors are believed to contribute to variation in the Hb level, including patient comorbidities and intercurrent events. Inflammation is also an important factor associated with Hb variability, and the consequences of persistent inflammatory activity are far-reaching in affected patients. This review addresses the complex role of inflammation in chronic kidney disease, as evidenced by the apparent state of deranged inflammatory markers. The mechanisms by which inflammatory cytokines may affect the response to ESAs, the development of anaemia and poor treatment outcomes are also examined. In addition, various options for intervention to enhance the response to ESAs in haemodialysis patients with inflammation are considered.

**Keywords:** anaemia management; chronic kidney disease; epoetin hyporesponsiveness; haemoglobin variability; inflammation

### Introduction

Anaemia management with erythropoiesis-stimulating agents (ESAs) is an important aspect of care for haemodialysis (HD) patients because anaemia is one of the common

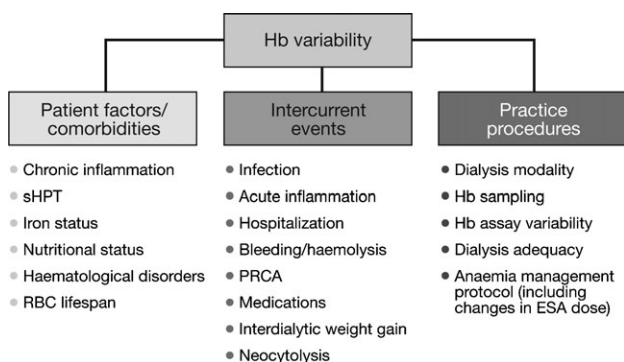
consequences of chronic kidney disease (CKD). The European Best Practice Guidelines (EBPG) for the management of anaemia of CKD specified that, within the recommended target range (at the time > 11 g/dL, not exceeding 12–14 g/dL), the exact patient target haemoglobin (Hb) level should be defined on an individual basis, taking into account gender, age, ethnicity, activity and comorbid conditions [1]. The importance of setting an upper limit for target Hb concentration was highlighted through the publication of results from the CREATE [2] and CHOIR [3] studies and a large meta-analysis [4]. Although the recommended target range has just been lowered to 10–12 g/dL as a result of the above study results [5,6], an individual patient’s demographic and disease characteristics, as well as comorbidities, continue to be an important consideration in determining target Hb. In HD patients, for example, higher Hb concentrations are particularly undesirable due to risks arising from post-dialysis haemoconcentration [7].

### Haemoglobin variability

At the individual patient level, Hb concentrations frequently exhibit a cyclical pattern over time such that a substantial proportion of dialysis patients receiving ESAs experience Hb levels both above and below the target range during a relatively short period of follow-up [8,9]. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective observational study that analysed anaemia management and outcomes in long-term HD patients from 12 countries, 83–94% of patients were receiving treatment with an ESA yet only 23–77% of patients in respective countries had a Hb concentration < 11 g/dL [10]. Similarly, Lacson *et al.* [8] reported that few patients maintained Hb in the target range in a study that measured variability in Hb level over 1 year in a large cohort of patients with end-stage renal disease (ESRD). Overall, only 38.4% of patients had Hb levels between 11 and 12 g/dL, while 12.2%, 31.5% and 30% of patients had Hb levels < 10 g/dL, < 11 g/dL and > 12 g/dL, respectively. Of note, at the time of these studies, the EBPG recommended treating patients until Hb reached > 11 g/dL with an upper limit of 12–14 g/dL [1].

While mean Hb levels may appear stable over time in any given population of dialysis patients, few individual

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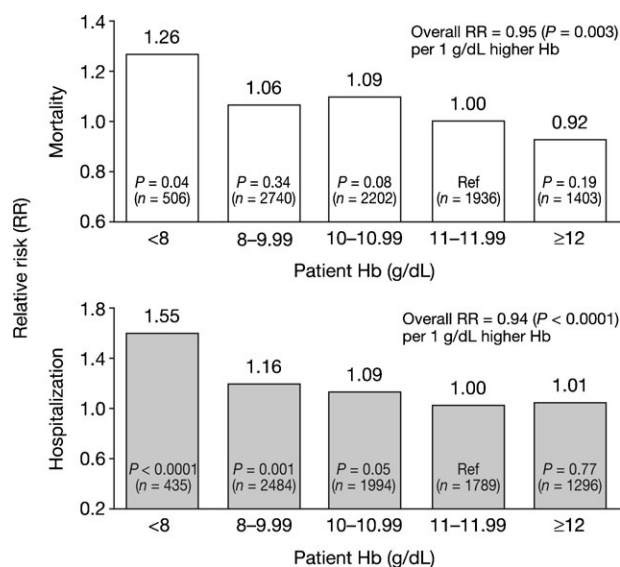


**Fig. 1.** Factors associated with Hb variability. Hb, haemoglobin; sHPT, secondary hyperparathyroidism; PRCA, pure red cell aplasia; RBC, red blood cell.

patients maintain stable Hb. Ebben *et al.* [9] measured Hb levels in a large cohort of patients for 6 months and found that the percentage of patients who were below, within and above the target range (defined as 11–12.5 g/dL at the time of study conduct) remained stable. However, this stability was not evident from individual data, as only a minority of patients (6.5%) had stable Hb levels over the study period, with nearly 90% exhibiting some pattern of Hb fluctuation [9,11]. A wide variety of factors have been associated with Hb variability, including patient factors, comorbidities, intercurrent events and practice procedures (Figure 1) [9,12–21]. This review will mainly address the impact of persistent inflammation on both Hb variability and responsiveness to ESAs in the treatment of anaemia of CKD. However, another intercurrent event worthy of mention is neocytolysis, the physiological process by which young circulating erythrocytes (neocytes) are selectively destroyed when red cell mass becomes excessive [15]. Evidence suggests that a greater understanding of this process may also help to optimize the treatment of these patients.

### Clinical consequences of haemoglobin variability

Recent studies have suggested an association of Hb variability with mortality, while other studies suggest that low Hb levels may be the critical factor associated with poor outcomes. In retrospective analyses of 34 963 HD patients, Yang *et al.* [22] and Brunelli *et al.* [23] found that a greater Hb variability was associated with diminished survival. However, the association was not evident in the subgroup of patients with Hb  $\geq 10.5$  g/dL, though this might have been due to the smaller size of this subgroup. Ebben *et al.* [9], in a much larger retrospective study of 152 846 patients, characterized six different types of Hb variability patterns and then evaluated hospitalizations and comorbidities in these categories. They observed that the group of patients with consistently low Hb levels had the highest percentage of hospitalizations and the highest number of comorbid conditions [9]. In a similar sample of 159 720 HD patients receiving epoetin, Gilbertson *et al.* found that the longer HD patients had a Hb level  $< 11$  g/dL, the greater their mortality risk ( $P < 0.001$ ) [11]. In another large retrospective study of HD patients, the proportion of time spent with



**Fig. 2.** Hb levels and risk for mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Hb, haemoglobin. Reprinted from [10], Copyright (2004), with permission from Elsevier.

Hb levels below a target of 11 g/dL was compared against the risk of death [24]. The results showed a clear trend of increased mortality with increasing time below this target level. For patients with Hb levels  $< 11$  g/dL for 80–100% of the time, the risk was  $\sim 1.8$  times as high as for patients with no time below this level. This trend was also observed in the DOPPS, where higher Hb values at the start of the study among patients on dialysis therapy for longer than 180 days were associated with a lower risk for mortality and hospitalization (Figure 2) [10]. These data suggest that maintaining patients within the target Hb range is an important goal in the treatment of renal anaemia.

### Computerized anaemia management to reduce haemoglobin variability

Given the importance of Hb stability in renal anaemia management, it is necessary to continue to both assess and refine target Hb ranges and to develop possible systematic processes for deciding how much and when to adjust doses of ESAs. In the last few years, considerable advances have been made in this area through computer-assisted implementation of treatment algorithms based on practice guidelines.

One such anaemia management system is known as the Leeds Algorithm, developed in Leeds, UK. Patient data, such as ESA and iron supplement doses, Hb levels, serum ferritin and iron status, are extracted from local hospital computerized patient records. Using these data, the Leeds Algorithm programme then provides recommendations for changes in ESA and iron dose, as appropriate, from an analysis against pre-determined thresholds. Richardson *et al.* [25] explored the consequences of setting different thresholds and ceilings for epoetin dose changes in two randomized, controlled studies in unselected HD patients. In one study, the dose of epoetin was increased when Hb levels

fell below either 10.5 g/dL or 11.5 g/dL in 236 patients followed up for 6 months. In the other study, the dose of epoetin was reduced at Hb levels above either 12 g/dL or 13 g/dL in 211 patients followed up for 8 months. Using this management system, a narrowing of the Hb level distribution could be achieved. Thus, the study demonstrated that the formal use of threshold and ceiling values for intervention using the Leeds Algorithm enabled the production of pre-specified Hb outcome distributions from the HD population. Gaweda *et al.* [26] also developed an algorithm, for model predictive control (MPC), using an artificial neural network model of Hb response to ESA treatment. Results showed that MPC of ESA administration may lead to an improvement in anaemia management.

### Haemoglobin variability as a consequence of inflammation

Evidence suggests that inflammation is an important factor associated with Hb variability and that high C-reactive protein (CRP) levels (a widely used surrogate marker of inflammatory activity) are a predictor for less stable Hb control in CKD patients. This was shown by Dellanna *et al.* [27] who analysed data from 225 HD patients in a retrospective, single-centre, 1-year longitudinal cohort study to determine risk factors associated with less stable Hb control in response to ESA treatment. In patients with <60% of mean monthly Hb levels > 11 g/dL, CRP values were higher ( $P < 0.0001$ ) than in patients with 61–100% of monthly Hb levels > 11 g/dL (Table 1). No significant differences were found between iron and dialysis parameters. Mueller *et al.* [28] conducted a study of similar design over 6 months in 1573 HD patients to determine patterns of Hb variability and contributing factors. As in the study by Dellanna *et al.* [27], lower average CRP values were associated with better Hb control ( $P < 0.0001$ ), and no significant differences regarding ferritin, transferrin saturation or dialysis parameters were found (the authors concluded that CRP was the only causal factor of Hb variability that they could observe) [28]. In a third study, Agarwal *et al.* [29] showed that S-albumin (another inflammatory marker) is also an important predictor of baseline Hb and sensitivity to ESAs.

Barany *et al.* [30] also sought to identify factors associated with Hb variability in prevalent HD patients.

**Table 1.** Association of Hb variability (expressed as percentage of mean monthly values > 11 g/dL over 1 year) with CRP levels and epoetin dose in 225 haemodialysis patients [27]

Time Hb > 11 g/dL (%)	n (%)	CRP (mg/dL)	Epoetin dose (IU/week)
81–100	120 (53.3)	1.3	5966
61–80	54 (24.0)	2.2	7510
41–60	34 (15.1)	2.7	10 163
21–40	12 (5.3)	2.9	10 947
0–20	5 (2.2)	2.4	13 357
Total	225 (100)	1.8	7407

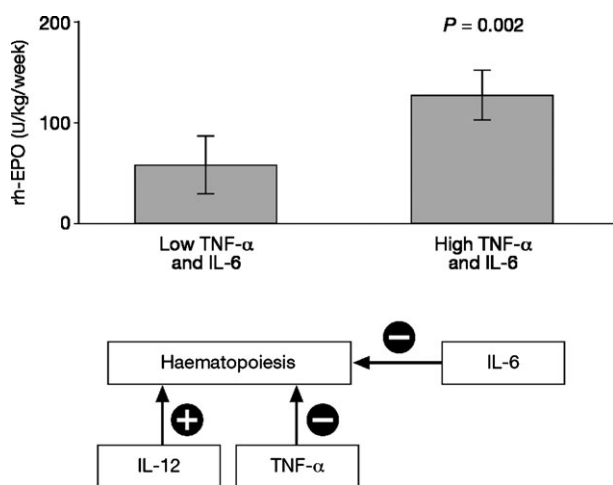
CRP, C-reactive protein; Hb, haemoglobin; IU, international units.  
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High-sensitivity CRP levels were recorded weekly, and Hb, interleukin-6 (IL-6), ferritin and percentage of hypochromic red cells (HRC) were recorded monthly in 228 patients during 3 months of follow-up. For each patient, the median and range values during the study were used for analysis. Two groups were formed whereby either all measurements of Hb levels were above the target value of 11 g/dL ( $n = 104$ ) or at least one measurement was below the target value ( $n = 124$ ). While comorbidity had no direct influence on Hb levels, significant correlations were found between Hb variation and CRP variation ( $P < 0.05$ ) and between HRC variation ( $P < 0.001$ ) and ferritin variation ( $P < 0.01$ ). HRC variation also correlated with IL-6 variation ( $P < 0.001$ ) and CRP variation ( $P < 0.001$ ). The associations between inflammatory markers and iron parameters in this study also suggested that inflammation had indirect effects on Hb variability via effects on iron metabolism.

### Consequences of inflammation on mortality

It has been recognized that more than 30–50% of patients with ESRD have serological evidence of an activated inflammatory response, as shown by increased levels of CRP and pro-inflammatory cytokines, such as IL-1, IL-6 and tumour necrosis factor (TNF- $\alpha$ ) [31–35]. These heightened levels of inflammatory markers are associated with reduced survival in these patients. This was demonstrated by Kalantar-Zadeh *et al.* [36] who measured serum levels of myeloperoxidase (MPO), an enzyme that is released during inflammation, at the start of a 3-year study in 356 patients undergoing maintenance HD. The adjusted hazard ratio for death for each 1000 pmol/L increase in MPO level was found to be 1.14 [95% confidence interval (CI) 1.03–1.26,  $P = 0.01$ ]. After dividing MPO values into tertiles, the hazard ratio for death of the highest tertile (versus the middle tertile) was 1.82% (95% CI 1.07–3.10,  $P = 0.03$ ). The link between MPO and inflammation was confirmed by the positive correlation between MPO and serum CRP values.

In the Modification of Diet in Renal Disease (MDRD) study, CRP was measured at baseline in 697 stage 3 and 4 CKD patients to examine the relationship of CRP levels (stratified into high CRP  $\geq 0.3$  mg/dL versus low CRP < 0.3 mg/dL) with cause of death [37]. High CRP was found to be an independent predictor of both all-cause mortality and cardiovascular mortality. Zimmermann *et al.* [38] and Qureshi *et al.* [39] were the first to show that overall mortality and cardiovascular mortality were significantly higher in patients with elevated CRP levels compared with those exhibiting normal CRP levels ( $P < 0.0001$ ) when they monitored outcome over a year in 280 HD patients. When Stenvinkel *et al.* [33] examined IL-6 levels in incident dialysis patients, they observed that elevated levels were significantly associated with poor outcome. When patient data were divided into quartiles according to basal levels of IL-6, the survival rate was shown to be statistically different between quartiles ( $P < 0.00001$ ). Thus, a link between inflammation and a higher risk of mortality has been established in numerous studies.



**Fig. 3.** Relationship between inflammatory cytokines and response to epoetin. IL, interleukin; rh-EPO, recombinant human erythropoietin; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ . Reprinted from [40] by permission from Macmillan Publishers Ltd.

### Consequences of inflammation on response to ESAs

A proportion of patients treated with ESAs respond poorly or not at all, and in a subset of these, no obvious cause (such as iron deficiency) can be found. Several studies have suggested that failure to respond to ESAs in CKD patients is due to enhanced immune activation that might suppress erythroid precursor cell production.

The interactions between different inflammatory mediators and ESA response appear to be complex. Furthermore, the patterns of cytokines and their interactions may be more important than individual circulatory plasma levels. In a study of 34 HD patients, Goicoechea *et al.* [40] found evidence for a relationship between deranged cytokine production and the required dose of epoetin. Epoetin responsiveness was linked to the levels of IL-6, TNF- $\alpha$  and IL-12. Patients with levels of TNF- $\alpha$   $\geq 2$  ng/mL and IL-6  $\geq 40$  ng/mL required a significantly higher dose of epoetin than patients with lower levels of these cytokines (128 U/kg/week versus 57 U/kg/week;  $P = 0.0024$ ) (Figure 3). Significant positive correlations between IL-6 and TNF- $\alpha$  production values and epoetin doses were observed ( $P = 0.039$  and  $P = 0.02$ , respectively). Conversely, there was a negative correlation between IL-12 production values and epoetin doses ( $P = 0.029$ ). Two other early studies showed a correlation between high levels of CRP and increased resistance to erythropoietin in HD patients [41,42]. Barany *et al.* [41] found that the weekly dose of epoetin in patients with a serum CRP level  $\geq 2$  mg/dL was on average 80% higher than the dose in patients whose serum CRP level was  $< 2$  mg/dL.

Another study investigated cross-sectional associations between inflammatory markers and the required dose of epoetin among 339 maintenance HD outpatients within a 13-week interval [43]. Serum concentrations of high-sensitivity CRP, IL-6 and TNF- $\alpha$  were observed to have a positive correlation with the required epoetin dose and

with an index of epoetin responsiveness (average weekly epoetin dose divided by the average Hb level).

In an Italian multicentre study, Locatelli *et al.* [44] examined the relationship between the natural logarithm of the weekly epoetin dose, normalized for post-dialysis body weight and outcome measures of nutrition or inflammation in 677 HD patients. Patients were categorized into four groups (untreated, hyperresponders, normoresponders and hyporesponders) on the basis of weekly epoetin dose requirement. Multiple linear regression analysis showed that CRP, Hb and serum iron levels were independently associated with the natural logarithm of the weekly epoetin dose. Median CRP level was higher in the hyporesponders than in the other groups (1.9 versus 0.8 mg/dL;  $P = 0.004$ ). The median weekly epoetin dose ranged from 30 IU/kg/week in the hyperresponsive group to 263 IU/kg/week in the hypo-responsive group. Ferritin levels were lower in the hyporesponders than in other patients (median 318 versus 445 ng/mL;  $P = 0.01$ ). Taken together, these findings support a clear association between epoetin hyporesponsiveness and either increased levels of CRP or iron deficiency in HD patients.

Further studies have shown that changes in inflammatory status contribute to both hyporesponsiveness to epoetin and variability of Hb levels in CKD patients. This was shown in a 6-month analysis (already described) of data from 1573 HD patients in a study conducted by Mueller *et al.* [28]. In addition to lower average CRP values, the patients with better controlled Hb levels (61–100% of mean monthly Hb values  $> 11$  g/dL) had lower average epoetin doses than the patients with poorly controlled Hb levels (0–60% of mean monthly Hb values  $> 11$  g/dL) [28].

In addition, a significant difference between epoetin dose ( $P < 0.0001$ ) and CRP level ( $P < 0.0001$ ) was observed in patients with a Hb change within 3 months of  $\geq 2$  g/dL versus  $< 2$  g/dL. Another recent study demonstrated the presence of the IL-6 polymorphism -174G, a genotype associated with increased secretion of IL-6, resulting in a requirement for higher doses of ESAs [45].

### Potential anaemic effects of pro-inflammatory cytokines

One link between elevated levels of pro-inflammatory cytokines and poor treatment outcomes in CKD patients may be the presence of anaemia. Evidence suggests several mechanisms by which inflammatory cytokines may affect the development of anaemia.

#### Suppression of bone marrow erythropoiesis

Many investigators have shown, using *in vivo* and *in vitro* studies, that cytokines can suppress erythroid progenitor cell proliferation. For example, IL-1 was shown to antagonize the capacity of epoetin to stimulate the proliferation of bone marrow erythroid precursors in culture [46], while serum from patients with both ESRD and inflammatory disease inhibited erythroid colony formation and response to epoetin, a process that was restored by the addition of

antibodies to TNF- $\alpha$  and interferon (IFN)- $\alpha$  [47]. Some studies, however, have failed to show a cytokine-mediated suppression of progenitor cell proliferation. In normal mice, for example, daily injections of IL-6 produced an increase in the number of progenitor cells in bone marrow [48]. In addition, other cytokines such as IL-12 have been shown *in vitro* to stimulate the growth of murine erythroid bone marrow progenitor cells [49].

#### *Suppression of erythropoietin production*

Erythropoietin levels in anaemic patients with chronic disorders, such as cancer, may be inappropriately low for the degree of anaemia, suggesting that erythropoietin deficiency may contribute to the development of this form of anaemia [50]. IL-1 $\alpha$ , IL-1 $\beta$  and TNF- $\alpha$  were shown to inhibit erythropoietin production in cultures of human hepatoma cell lines [51], and to cause dose-dependent inhibition of hypoxia-induced erythropoietin production in the cell line Hep3b [52]. Another study showed, however, that the epoetin response did not differ between rats with both acute inflammation and anaemia and control animals with a comparable degree of anaemia [53].

#### *Increased intestinal bleeding*

IL-6, when administered intraperitoneally to rats, was found to be associated with blood loss in intestinal tissue using erythrocyte labelling with <sup>99m</sup>technetium, as well as a marked decrease in Hb levels [54]. In this study, no evidence was found for suppression of bone marrow erythropoiesis.

#### *Modulation of iron metabolism*

Anaemia of inflammation is characterized by decreased iron and iron-binding capacity (transferrin), increased ferritin and the presence of iron in bone marrow macrophages, indicating impaired mobilization of iron from stores. In general, cytokines may impair iron metabolism, leading to functional iron deficiency, via several different mechanisms. First, high doses of ESAs may overstimulate erythropoiesis to exceed the maximum capacity of liver iron stores. Secondly, increased ferritin and decreased transferrin production shunt iron to the reticulo-endothelial storage pool, preventing delivery to erythroid precursors. In addition, mucosal uptake and mucosal transfer of iron have been shown to be significantly reduced in HD patients with increased CRP levels (>8 mg/L versus <8 mg/L,  $P < 0.01$ ) [55]. Patients with increased CRP levels had significantly higher serum ferritin concentration ( $P < 0.02$ ), lower serum transferrin concentrations ( $P < 0.01$ ) and required higher epoetin doses to maintain a stable haematocrit between 30% and 35% ( $P < 0.05$ ), confirming the pattern of functional iron deficiency in the anaemia of inflammation.

Recently, hepcidin, the hormone responsible for iron homeostasis, has emerged as a key mediator responsible for the disturbed iron metabolism in the anaemia of CKD [56]. Synthesized in the liver, hepcidin acts by controlling intestinal iron uptake and retention of iron in macrophages engaged in the recycling of iron from senes-

cent erythrocytes. Specifically, hepcidin has been shown to bind to ferroportin, a transmembrane protein that is the sole known cellular exporter of iron. After binding, ferroportin is internalized and degraded, leading to the decreased export of iron and cellular iron retention [57,58]. Thus, the hepcidin–ferroportin interaction determines serum iron concentrations.

Hepcidin expression is regulated in response to various stimuli. Synthesis of hepcidin increases in response to iron overload [59] and decreases in response to anaemia, hypoxia and erythropoiesis [60,61]. Hepcidin expression is also up-regulated during infections and inflammation, contributing to hypoferraemia and limitation of iron supply to the bone marrow (independent of iron status or erythropoietic activity) [56]. The IL-6 inflammatory cytokine, released during the inflammatory process, was shown to correlate with dramatically increased hepcidin gene expression both in mice and humans [62]. In patients with renal insufficiency (likely due to the low-grade inflammation in these patients), elevated levels of both the hepcidin precursor pro-hepcidin [63–65] and hepcidin [66] have been detected, and have been hypothesized to be responsible for the iron deficiency and anaemia seen in these patients. Thus, hepcidin may link inflammation and anaemia, acting as an indicator of functional iron deficiency [56,60,67]. The contribution of hepcidin to the aetiology of resistance to ESA therapy remains to be established.

The available evidence suggests that CKD is a state of increased pro-inflammatory cytokine activity that might suppress erythroid progenitor cell production leading to hyporesponsiveness to ESAs and poor treatment outcomes. Understanding the influence of inflammatory cytokines on erythropoietin production will hopefully provide clarification of the complex interplay between multiple factors involved in the pathogenesis of the anaemia of CKD. Possible future pharmacological interventions for inflammation-associated hyporesponsiveness to ESA treatment include anti-cytokine and anti-oxidative treatment strategies.

### **Interventions for ESRD patients with inflammation**

A number of possible strategies exist to enhance the response to ESAs and iron in ESRD patients with persistent low-grade inflammation. Despite the high prevalence of chronic inflammation in CKD, some basic tenets regarding the treatment of inflammation are obvious and apply to all patients regardless of whether or not they are on dialysis. Occult infections, when found, should be treated with antibiotics. Also, occult infection of old, non-functioning, arteriovenous grafts (AVGs) is a common cause of ESA resistance and a chronic inflammatory state in HD patients. Resection of old non-functioning AVGs with occult infection is associated with the resolution of markers of a chronic inflammatory state and improvement in responsiveness to ESA treatment [68]. Optimal treatment of chronic heart failure is essential as it may cause, or contribute to, an inflammatory state [69]. Chronic heart failure with fluid

overload, a common feature in dialysis patients, may be an important cause of inflammation. Thus, rigorous measures should be taken to avoid or treat fluid overload in these patients [31].

### Optimization of the dialysis procedure

The available evidence suggests that the HD procedure itself may cause an inflammatory response and that using biocompatible membranes [70] and ultrapure dialysate [71] can reduce such a response. As new and more biocompatible peritoneal dialysis solutions become available, they should be considered in peritoneal dialysis patients with signs of inflammation. In addition, evidence suggests that the dialysis schedule may have an impact on the levels of inflammatory markers. Ayus *et al.* [72] showed, in a non-randomized clinical trial, that compared with conventional HD (three 4-h sessions per week), short daily dialysis (six 3-h sessions per week) was associated with a reduction in the levels of inflammatory markers and left ventricular hypertrophy.

In a recent study, patients receiving on-line haemofiltration, which removes a wide spectrum of uraemic toxins, exhibited micro-inflammation to a lesser degree than patients on high-flux HD [73]. On-line haemofiltration combines convective transport, for the removal of large solutes, with diffusion, for the removal of small solutes. The study also demonstrated a correlation between increased inflammation and induction of endothelial damage in HD patients. Thus, optimizing the dialysis procedure may be important to decrease the prevalence of inflammation in HD patients.

### Immune modulation

Pentoxifylline, a drug traditionally used in the treatment of peripheral vascular disease because of its potent haemorrhological properties, was found to have anti-inflammatory properties *in vitro*. From this observation, Cooper *et al.* [74] hypothesized that pentoxifylline might improve the response to ESAs in anaemic CKD patients by inhibiting pro-inflammatory cytokine production *in vivo* to give rise to enhanced erythropoiesis. A total of 12 patients with ESRD and ESA-resistant anaemia completed treatment with oral pentoxifylline for 4 months. At the end of the treatment period, the mean Hb concentration significantly increased ( $P = 0.0001$ ), *ex vivo* T-cell expression of TNF- $\alpha$  significantly decreased ( $P = 0.0007$ ) (Figure 4) and IFN- $\gamma$  expression decreased ( $P = 0.0002$ ) from baseline levels. Thus, pentoxifylline therapy had significantly improved the Hb response in patients with previously ESA-resistant anaemia in renal failure. The authors concluded that this might have occurred due to inhibition of pro-inflammatory cytokine production, which could interfere with the effectiveness of ESA treatment.

### Anti-oxidant treatment

As oxidation products may promote persistent inflammation in uraemia, the use of anti-oxidants, such as vitamin E,

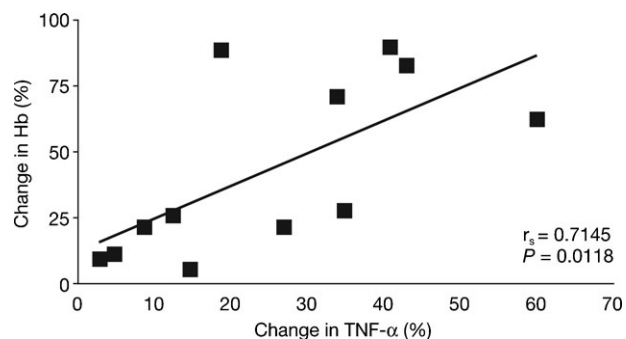


Fig. 4. Correlation between change in TNF- $\alpha$  and Hb in patients treated with pentoxifylline [74]. Hb, haemoglobin; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ .

which can modulate cytokine biology, is of particular interest. Indeed, vitamin E supplementation improved the therapeutic effect of ESA treatment in children with CKD [75]. In this study, the efficacy of combined therapy with epoetin and vitamin E versus epoetin alone in the treatment of anaemia was examined in 10 children on chronic HD. Vitamin E was introduced after 2 weeks of epoetin monotherapy, when the signs of acute oxidative stress appeared. After 2 weeks of vitamin E treatment, there was a considerable decrease in indices of oxidative stress compared with epoetin monotherapy. A significant increase in Hb and haematocrit ( $P < 0.01$ ) was achieved within 2 weeks of starting the combined therapy, while similar results occurred only at the fifth and eighth weeks without vitamin E. In another study, HD using vitamin E-modified dialysis membranes in ESA-treated patients also improved anaemia, and this appeared to be a direct consequence of the concentration-dependent effect of plasma vitamin E in improving red blood cell survival [76]. As present data in the literature are based on small patient cohorts, larger prospective randomized trials will be needed to determine whether anti-oxidative treatment strategies are beneficial to the anaemic CKD patient with inflammation.

### Resection of failed kidney transplants

It has been common practice not to remove failed kidney transplants. However, evidence now suggests that the presence of a failed kidney transplant in HD patients may be associated with a chronic inflammatory state. This in turn can result in resistance to ESAs. In a study by Lopez-Gomez *et al.* [77], resection of failed kidney transplants led to a significant decrease in levels of inflammatory markers.

### Conclusion

Persistent inflammation may contribute to the variability in Hb levels and hyporesponsiveness often seen in CKD patients. This variability, or perhaps more specifically, Hb variability in which Hb values are often below target range, may be associated with increased morbidity and

mortality in these patients. Recently developed computerized anaemia management systems may offer one opportunity to control Hb concentrations within the target range, providing physicians with a basis to treat patients in an objective and systematic manner. These computerized systems are likely to grow in importance and benefit, and should lead to better and simpler patient management in the future.

The available evidence suggests that CKD is a state of increased pro-inflammatory cytokine activity, which might suppress erythroid progenitor cell production leading to hyporesponsiveness to ESAs and poor treatment outcomes. Understanding the influence of inflammatory cytokines on erythropoietin production and hepcidin synthesis will hopefully clarify the interplay of the multiple factors involved in the pathogenesis of the anaemia of chronic disease. Possible future pharmacological interventions for inflammation-associated hyporesponsiveness to ESA therapy include anti-cytokine and anti-oxidative treatment strategies.

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