APCN x TSN 2025
23rd Asian Pacific Congress of Nephrology
Dec. 5 Fri. ▸ Dec. 7 Sun., 2025 TaiNEX 2, Taipei, Taiwan

Mighty Hallym
한림대학교성심병원

Management of ESA hyporesponsiveness
- Focusing on inflammation

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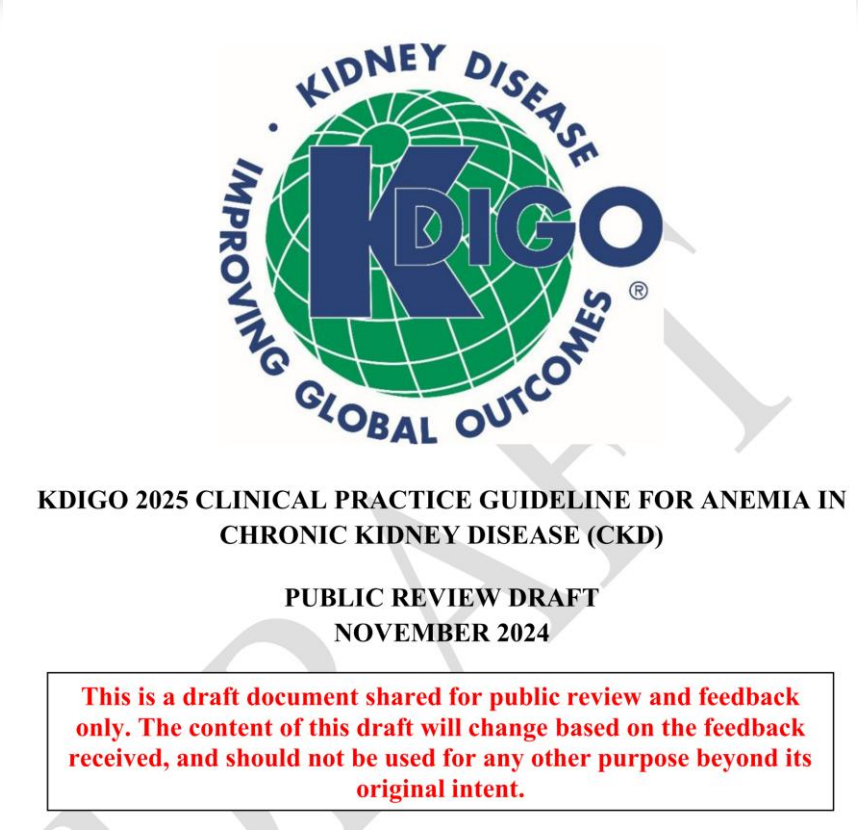
- Definition
- Inflammation
- Management options



Definition of ESA hyporesponsiveness

- Definition vary across guidelines based on numerical values of ESA thresholds.
- CKD patients who fail to achieve target Hb despite a significant and sustained increase in ESA doses.
- Prevalence: 12.5~30.3%.
- Acute or Chronic (>4 months), Difficult to treat dynamic condition, mostly transient

Definitions of ESA hyporesponsiveness	Organization or study
Weight-adjusted ESA resistance index (ERI) [weekly ESA dose/(body weight x Hb) > 15.4 IU/kg x g/dl (quartile IV)*	Panichi et al. RISCAVID study, 2011[271]
Failure to achieve target Hb levels with epoetin doses greater than: - i.v. EPO 450 IU/kg/week, - s.c. EPO: 300 IU/kg/week, - darbepoetin dose >1.5 µg/kg/week	The Renal Association, UK, 2017, 2020[281]
Failure to achieve Hb target: People receiving HD: Despite 3000 IU/dose of i.v. rHuEPO 3x/ week (9000 IU/week) or 60 µg/week of i.v. darbepoetin alfa once per week People receiving PD: Despite 6000 IU/dose of s.c. rHuEPO once per week (6000 IU/week) or 60 µg/week of i.v. darbepoetin alfa once per week Predialysis people with CKD: Despite 6000 IU/dose of s.c. rHuEPO once per week (6000 IU/week)	Japanese Society for Dialysis Therapy, 2015[282]

ESA hyporesponsiveness

NICE 2021 [26] and BRA 2017 [27]	An aspirational HgB range is not achieved despite treatment with 300 IU/kg/week or more of subcutaneous epoetin or 450 IU/kg/week or more of intravenous epoetin or 1.5 µg/kg/week of darbepoetin Or There is a continued need for the administration of high doses of ESAs to maintain the aspirational HgB range

- In general, for a 60kg CKD patient, ➔ more than 90 mcg/week of darbepoetin.

- Weight-adjusted ESA resistance index (ERI)

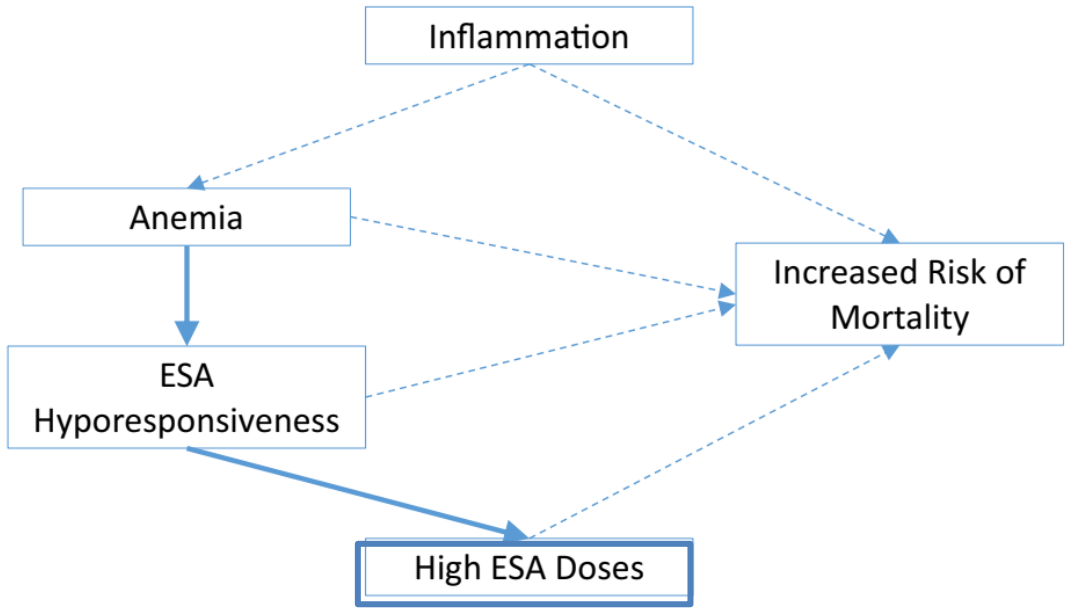
Erythropoietin Resistance Index (ERI) Calculation

$$\text{ERI} = \frac{\text{Weekly erythropoietin dose}}{(\text{Weight} \times \text{Hemoglobin})}$$

- Normal: ERI < 10
- High: ERI ≥ 15

Why important?

- Unresolved symptoms – fatigue, dyspnea, general weakness.
- Hidden causes!
- Higher ESA dose: higher risk for adverse CV outcome, kidney failure risk, and **mortality**.
  - - Numerous previous data demonstrated that higher ESA doses, independent of hemoglobin level, were associated with increased risk for death.



Causes of ESA hyporesponsiveness

Risk factor	Responding treatment
Iron deficiency • Absolute • Functional	Iron supplementation, treat cause of blood loss. Address other factors, i.e., inflammation and uremia, which may have led to functional iron deficiency. IV iron required for functional iron deficiency
Inflammation and hepcidin accumulation	Address likely cause of inflammation, i.e., antibiotics for acute infection and steroid treatment for systemic inflammation. To lower serum hepcidin production and accumulation, rule out sources of infection from catheter and graft access
Uremia	Increased uremic clearance; adequate dialysis delivery – increased dialysis intensity and dialysate flow, e.g., convective HD; and improved membrane permeability
CKD-MBD • Vitamin D deficiency • Secondary hyperparathyroidism • Other CKD-MBD factors – elevated FGF-23, ALP	Vitamin D supplementation (native and activated), calcimimetics, low-phosphate diet, and phosphate binders. Consider parathyroidectomy if refractory to medical treatment
Non-iron malnutrition • Folic acid deficiency • Vitamin C deficiency • Copper deficiency • α-Lipoic acid deficiency • L-Carnitine deficiency • Other non-iron malnutrition factors – PEW, vitamin B_6 deficiency, vitamin B_{12} deficiency	Nutritional supplementation to address the cause of non-iron nutritional deficiency
Other factors of ESA hyporesponsiveness • Drug-induced factors – ACEi, ARB • Malignancy • Primary bone marrow and myelosuppressive disorders • Antibody-mediated pure red cell aplasia • Aluminum overload	Reduce dose or hold ACE inhibitor and ARBs Treat underlying oncological or hematological cause, and reduce its associated complications Anti-ESA treatment if indicated Supportive treatment for aluminum overload

ACD

- The causes of ESA hyporesponsiveness cannot be identified in approximately 30%.

Kidney Dis 2022;8:103–114

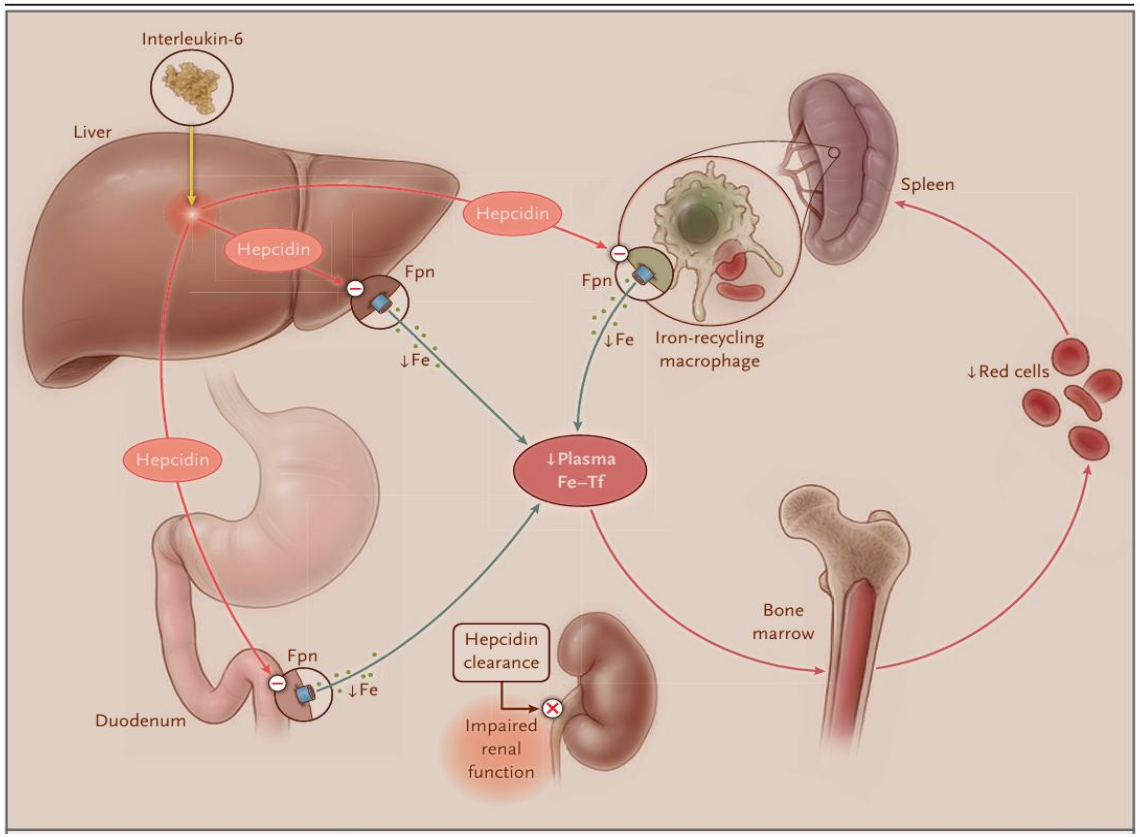
Targeting inflammation

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Anemia of Inflammation

Tomas Ganz, Ph.D., M.D.



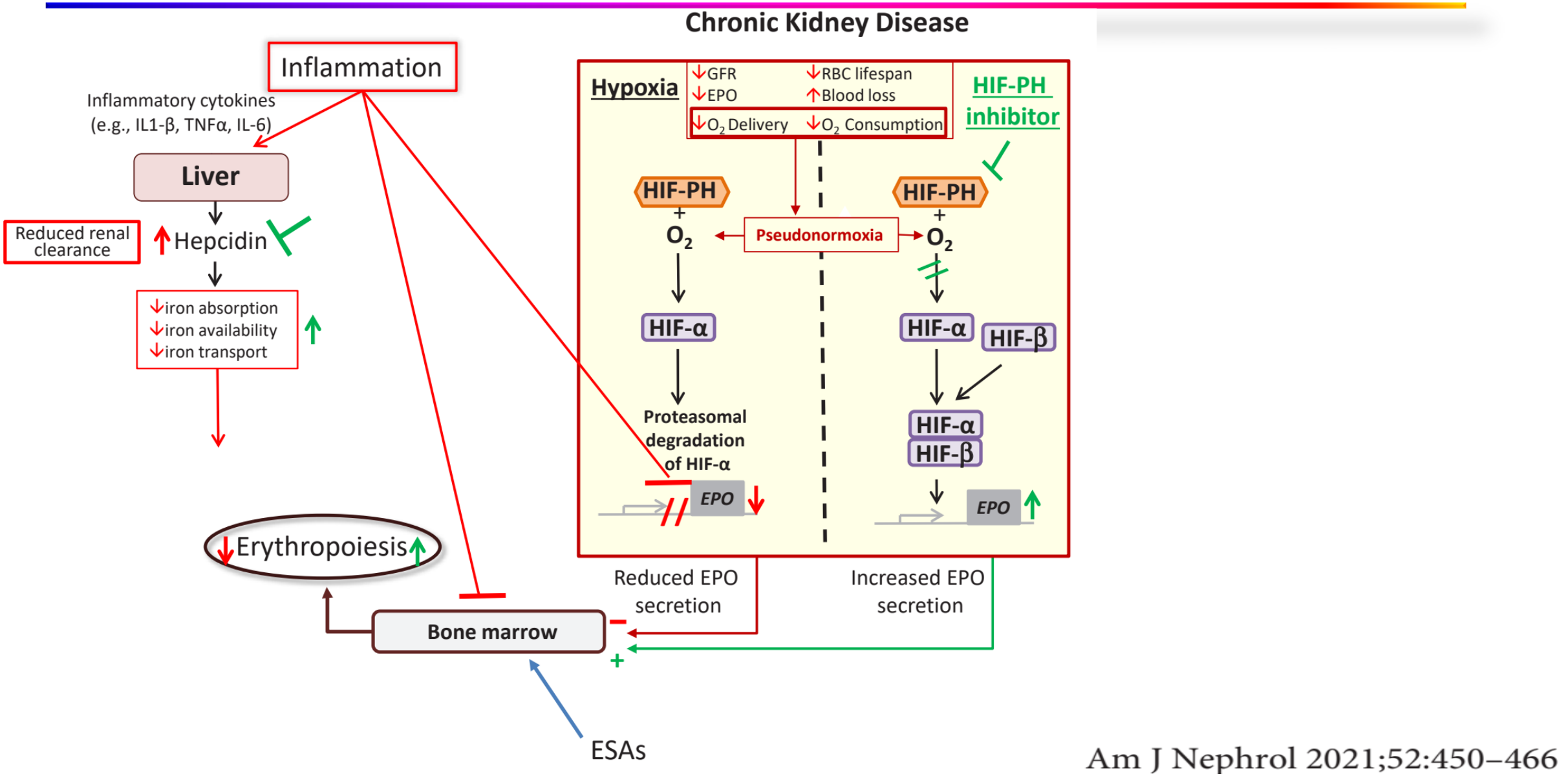
Hepcidin-fpn axis: key target!

Table 2. Compounds under Development for the Treatment of Anemia of Inflammation.

Compound	Target*	Stage of Development (Study)
Heparin derivatives	BMPs that stimulate hepcidin synthesis	Preclinical stage (Poli et al.[57])
Soluble hemojuvelin	BMPs that stimulate hepcidin synthesis	Preclinical stage (Theurl et al.[58])
Engineered hepcidin binders	Hepcidin	Preclinical stage (Hohlbaum et al.[59]) and phase 1 (Boyce et al.[60])
Monoclonal antibodies	Ferroportin, blocking hepcidin access	Phase 1 (Sheetz et al.[61])
	BMP-6	Phase 1 (Sheetz et al.[61])
	Hepcidin	Phase 1 (Vadhan-Raj et al.[62]) and preclinical stage (Sasu et al.[63])
	Hemojuvelin	Preclinical stage (Kovac et al.[64])
Momelotinib	BMP receptor (ACVR1) and JAK1 and JAK2	Preclinical stage (Asshoff et al.[65]) and phase 3 (Mesa et al.[66])†
TP-0184	BMP receptor (ACVR1)	Phase 1 (Peterson et al.[67])
Prolyl hydroxylase inhibitors	HIF prolyl hydroxylases	Preclinical stage (Barrett et al.[68]) and phase 2 (Chen et al.[69])‡

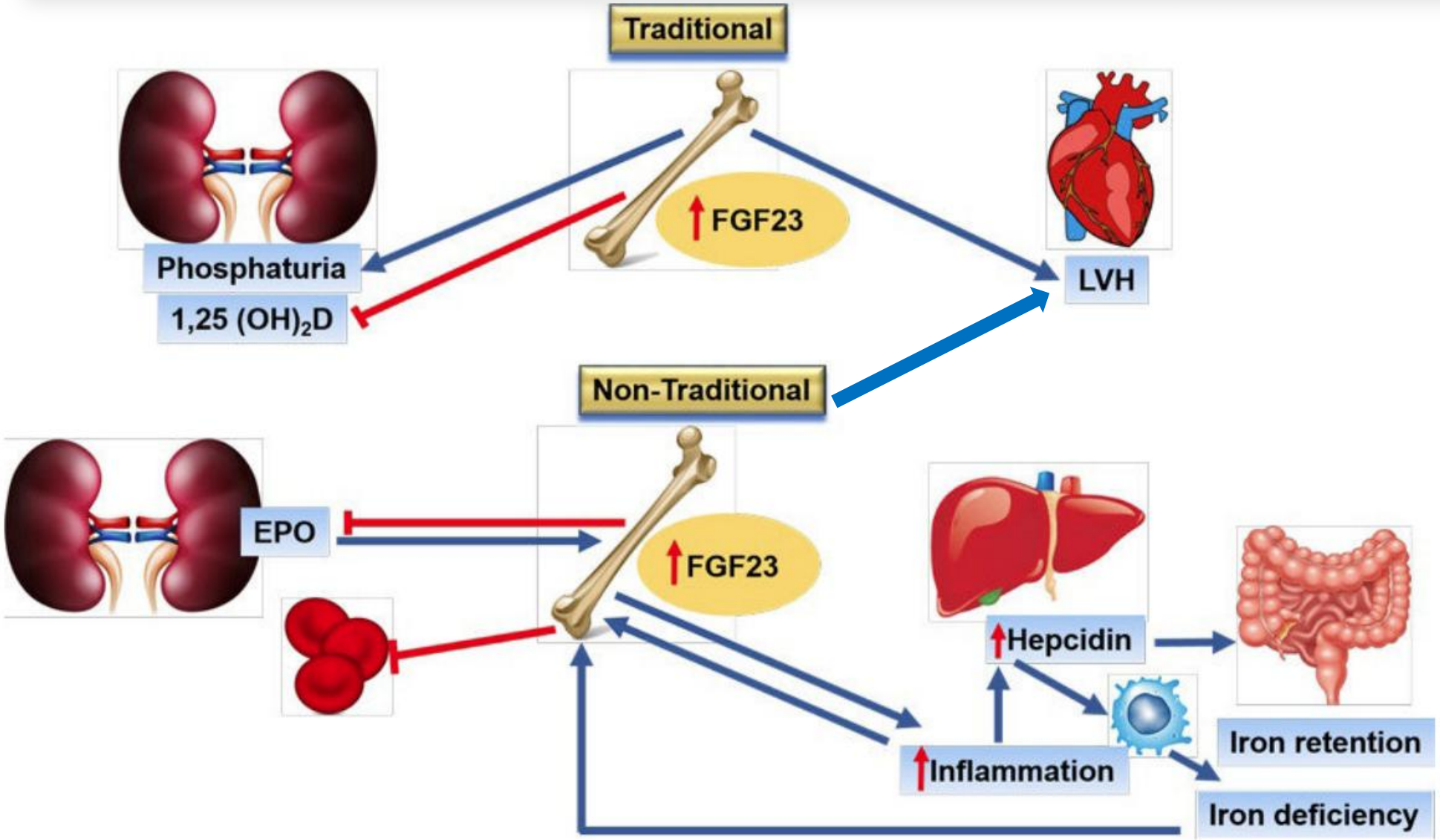
N Engl J Med 2019;381:1148-57.

Inflammation and anemia



Am J Nephrol 2021;52:450–466

Inflammation and FGF23



How to treat ESA Hyporesponsiveness?

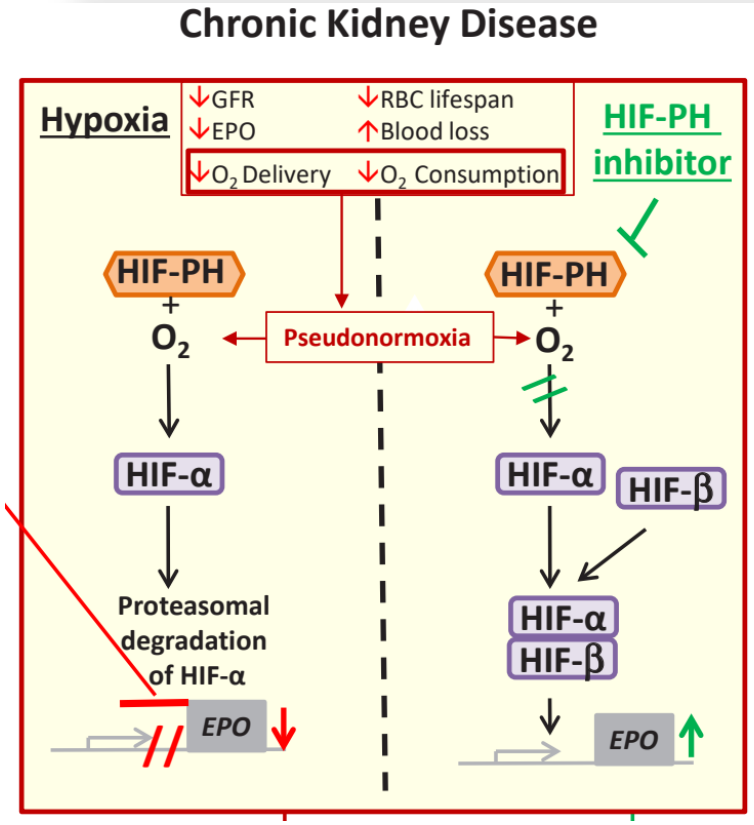
- Improve functional iron deficiency
- Use of HIF-PHI (HIF stabilizer)
- Can we control circulating hepcidin level?
- Can we treat high inflammatory status in CKD?

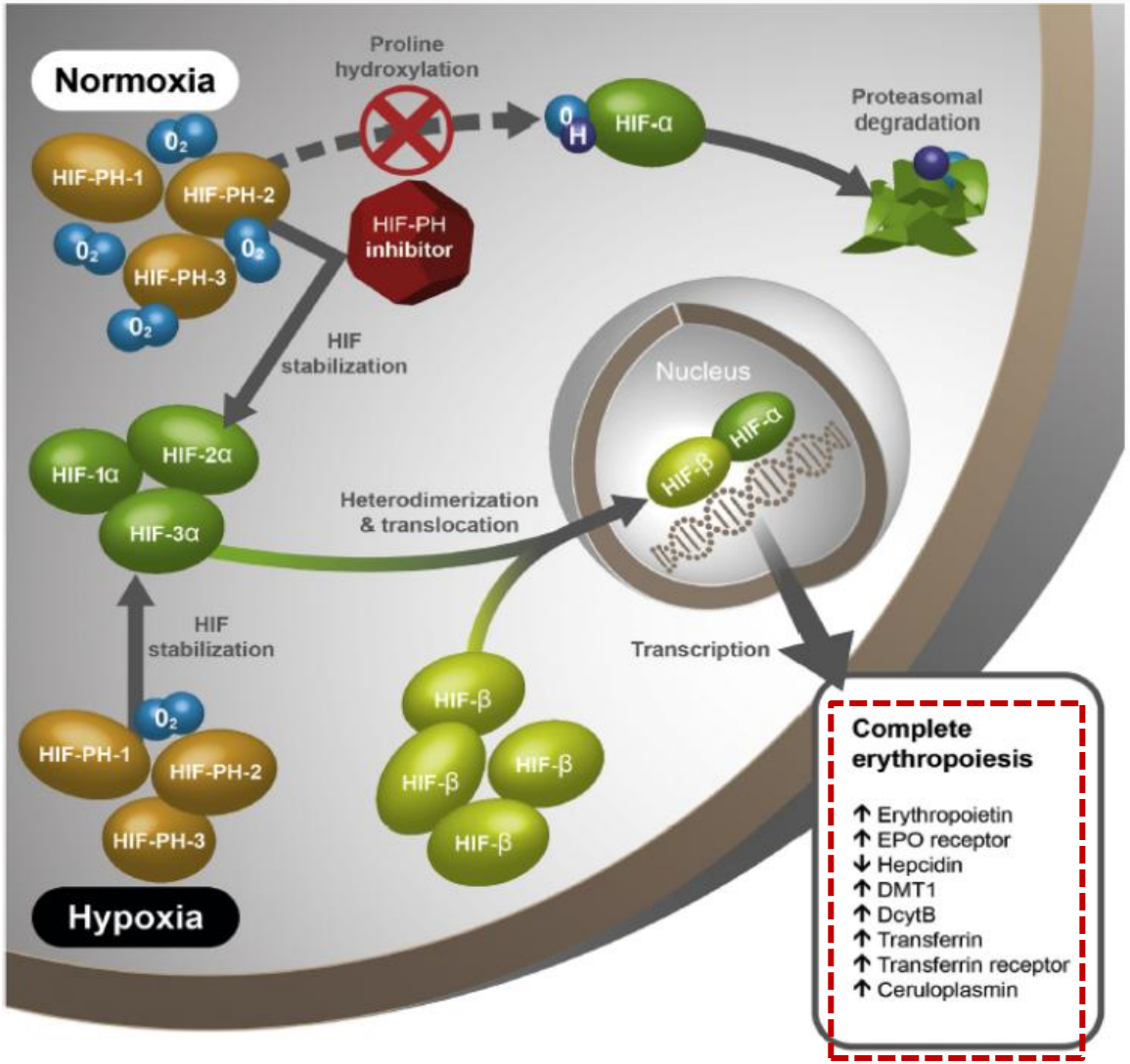
How to treat ESA Hyporesponsiveness?

- **Improve functional iron deficiency**
- Use of HIF-PHI (HIF stabilizer)
- Can we control circulating hepcidin level?
- Can we treat high inflammatory status in CKD?

- In 2025 draft: "**iron-restricted erythropoiesis.**"
- TSAT < 20% and ferritin over 100-200 µg/L.
- CKD5D: anemia + ferritin ≤ 500 µg/L, TSAT ≤ 30%
- IV >> PO (in inflammatory condition)
- Upper level: 700 µg/L or TSAT 40%

HIF-PHI





- Endogenous EPO release
  - ➔ much lower increases in serum erythropoietin levels than ESAs
  - ➔ more physiologic, avoid side effects
- Improved iron availability.

Am J Nephrol 2021;52:450–466

HIF PHI (approved for marketing as of Oct 2024)

HIF-PHI	Recommended dosing for treatment initiation	Maximum daily dose	Dose frequency	Drug metabolism and transport	Approved for marketing in (as of May 2024):
Daprodustat	CKD not receiving dialysis: 2–~4 mg (ESA-naïve), 4 mg (switch from ESA) CKD G5D: [Japan] 4 mg, [U.S.] 1–~4 mg (ESA-naïve), 4–12 mg (switch from ESA)	24 mg	daily	CYP2C8[254]	Japan, U.S.*
Roxadustat	CKD not receiving dialysis and CKD G5D (ESA-naïve): [EU] 70 mg for body weight <100 kg, 100 mg for body weight ≥100 kg CKD not receiving dialysis (switch from ESA): [EU] 70–200 mg, [Japan] 50 mg (ESA-naïve), 70–100 mg (switch from ESA)	3.0 mg/kg body weight	3 times per week	CYP2C8, UGT1A9, BCRP, OATP1B1, OAT1, OAT3[230] inhibitor of: CYP2C8, BCRP, OATP1B1, OAT3[230, 258]	China, Chile, Egypt, EU, Iceland, Japan, Kuwait, Lichtenstein, Mexico, Norway, Russia, Saudi Arabia, South Africa, South, Korea, Turkey, UAE, UK
Vadadustat	300 mg (ESA-naïve and switch from ESA)	600 mg	daily	UGT1A1, 1A7, 1A8, 1A9, BCRP, OAT3[259] inhibitor of CYP2C8 (in vitro), BCRP, OAT3 and inducer of CYP2B6 (in vitro)[259, 260]	Australia, EU, Japan, Korea, Taiwan, U.S.†

Use of HIF PHI: still very cautious in KDIGO 2025 draft

Practice Point 3.7.1: In people with anemia and CKD G5D and CKD not receiving dialysis with initial or subsequent ESA hyporesponsiveness**, identify and treat the underlying causes** of ESA hyporesponsiveness, if possible.

Practice Point 3.7.2: In people with CKD, anemia, and ESA hyporesponsiveness, if there is a desire to raise the Hb to avoid a transfusion or improve symptoms attributable to anemia, a trial of HIF-PHI may be considered after discussion of **potential risks and benefits prior to treatment.**

Practice Point 3.7.3: In patients with anemia and CKD, if a decision is made to use HIF-PHI for the treatment of ESA hyporesponsiveness, **the Hb should be raised to the lowest level** that alleviates anemia-related symptoms or which reduces the risk of requiring an RBC transfusion to an acceptable level.

Practice Point 3.7.4: In patients with CKD, anemia, and ESA hyporesponsiveness**,** if a desired erythropoietic response has not been achieved **after 3–4 months of initiating a trial of HIF-PHI, discontinue treatment.**

Consider 3–4 month trial of a HIF-PHI and/or transfuse as clinically indicated

Practice Point 3.7.5: In people with anemia and CKD not receiving dialysis or with CKD G5D who have **active malignancy, a recent CV event, or recent vascular thrombosis do not use HIF-PHI.**

Targeting IL-6

Clinical Trial > Am J Kidney Dis. 2005 Feb;45(2):324-33. doi: 10.1053/j.ajkd.2004.09.018.

Plasma interleukin-6 predicts cardiovascular mortality in hemodialysis patients

Madhumathi Rao [1], Daqing Guo, Mary C Perianayagam, Hocine Tighiouart, Bertrand L Jaber, Brian J G Pereira, Vaidyanathapuram S Balakrishnan

Affiliations + expand

PMID: 15685511 DOI: 10.1053/j.ajkd.2004.09.018

Abstract

Background: Interleukin-6 (IL-6) is a mediator and marker of the chronic inflammatory process that is responsible for much of the morbidity and mortality seen in hemodialysis (HD) patients. This study evaluated circulating plasma IL-6 as a predictor of all-cause mortality and cardiovascular mortality and studied its relationship to prevalent comorbidity and hypoalbuminemia, in a cohort of stable HD patients enrolled in the HEMO study.

Methods: Clinical data included demographic, medical, and routine laboratory parameters. Comorbidities were graded using the Index of Co-Existing Diseases (ICED). Outcomes of interest were all-cause mortality and cardiovascular mortality. Blood samples were drawn at enrollment and annually, and plasma IL-6 levels measured with high-sensitivity enzyme-linked immunosorbent assay.

Results: Median plasma IL-6 level in 206 patients was 7.9 pg/mL (range, 0.1 to 90.3 pg/mL) and was higher in patients with vascular disease (P = 0.03), higher ICED scores (P = 0.01), and lower Karnofsky indices (P < 0.01). Serum albumin was inversely related to plasma IL-6 levels (P = 0.03, r = -0.16). Unadjusted median survival time was 1,209 days in the lowest quartile of plasma IL-6 and 806 days in the highest (P = 0.02, log rank test). A 1-log increase in plasma IL-6 was associated with a 1.19-fold higher adjusted risk for all-cause mortality (P = 0.04; 95% confidence interval, 1.01 to 1.40) and a 1.43-fold higher adjusted risk of cardiovascular mortality (P = 0.02; 95% confidence interval, 1.06 to 1.92). Hazard ratio estimates were higher when IL-6 levels over time were incorporated as a time-dependent covariate.

Conclusion: Plasma IL-6 levels are strongly associated with comorbidity in HD patients and are a powerful predictor of cardiovascular and all-cause mortality.

> Kidney Int. 2010 Mar;77(6):550-6. doi: 10.1038/ki.2009.503. Epub 2009 Dec 16.

Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease

Daniela V Barreto [1], Fellype C Barreto, Sophie Liabeuf, Mohammed Temmar, Horst-Dieter Lemke, Christophe Tribouilloy, Gabriel Choukroun, Raymond Vanholder, Ziad A Massy; European Uremic Toxin Work Group (EUTox)

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PMID: 20016471 DOI: 10.1038/ki.2009.503

Free article

Abstract

Chronic inflammation associated with chronic kidney disease predicts all-cause and cardiovascular mortality in hemodialysis patients. Here we sought to evaluate the association between plasma levels of the inflammatory mediator interleukin-6 (IL-6) and mortality and aortic calcification/stiffness in 125 patients at different stages (2-5D) of chronic kidney disease. Using multivariate linear regression, we found that plasma IL-6 was independently associated with C-reactive protein, albumin and the stage of chronic kidney disease, but not the aortic calcification score or pulse wave velocity. During follow-up studies (median of 829 days), 38 patients died, 22 from cardiovascular events. Plasma IL-6 significantly predicted overall and cardiovascular mortality; this association persisted after multiple adjustments or restricting the analysis to pre-dialysis patients. Moreover, IL-6 was a significantly better predictor of mortality than C-reactive protein, albumin or tumor necrosis factor-alpha. Hence, plasma IL-6 independently predicted overall and cardiovascular mortality in patients at different stages of chronic kidney disease; however, whether lowering plasma IL-6 will affect the outcome of chronic kidney disease will require more direct evaluation.

Targeting IL-6 (RESCUE phase 2)

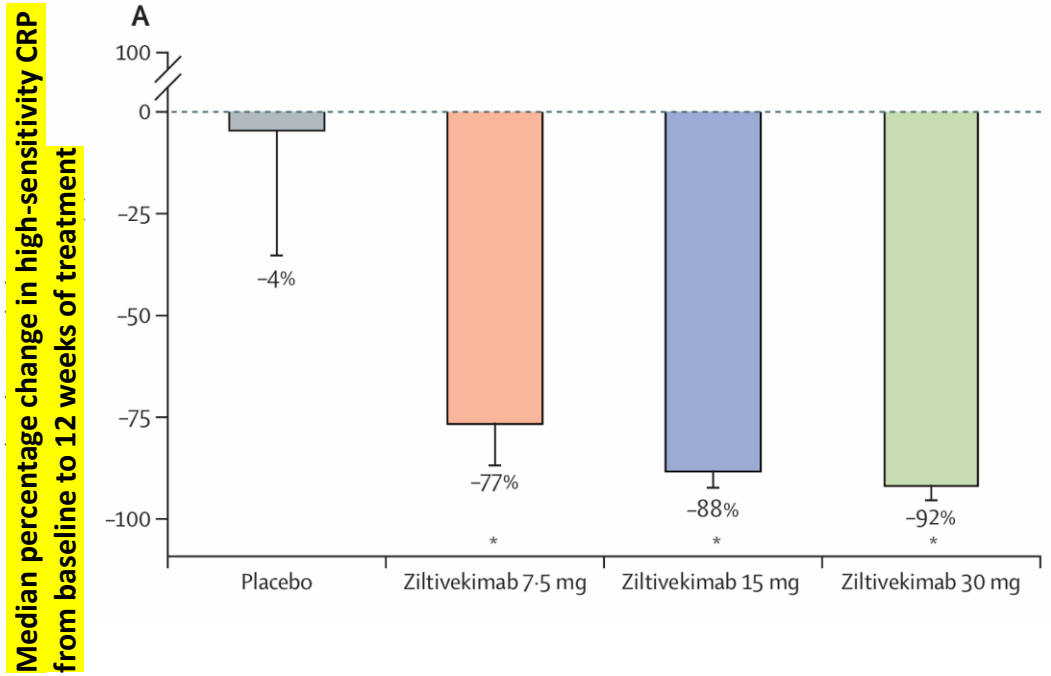
IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial

*Paul M Ridker, Matt Devalaraja, Florian M M Baeres, Mads D M Engelmann, G Kees Hovingh, Milana Ivkovic, Larry Lo, Douglas Kling, Pablo Pergola, Dominic Raj, Peter Libby, Michael Davidson, on behalf of the RESCUE Investigators**

Lancet 2021; 397: 2060–69

- Ziltivekimab, a fully human monoclonal antibody directed against the IL-6 ligand
- 264 CKD stage 3-5 and systemic inflammation (hscRP ≥2 mg/L)

	Placebo (n=66)	Ziltivekimab 7·5 mg (n=66)	Ziltivekimab 15 mg (n=66)	Ziltivekimab 30 mg (n=66)
Age, years	66·0 (60·0–74·0)	70·0 (60·0–74·0)	65·5 (59·0–74·0)	68·0 (61·0–76·0)
Gender				
Female	29 (44%)	32 (48%)	36 (55%)	32 (48%)
Male	37 (56%)	34 (52%)	30 (45%)	34 (52%)
Diabetes*	50 (76%)	41 (62%)	48 (73%)	48 (73%)
Hypertension†	62 (94%)	60 (91%)	60 (91%)	60 (91%)
Atherosclerotic cardiovascular disease	37 (56%)	29 (44%)	27 (41%)	33 (50%)
Statin use	45 (68%)	44 (67%)	45 (68%)	45 (68%)
Chronic kidney disease stage‡				
3a	19 (29%)	16 (24%)	23 (35%)	19 (29%)
3b	23 (35%)	30 (45%)	29 (44%)	26 (39%)
4	17 (26%)	16 (24%)	10 (15%)	17 (26%)
5	5 (8%)	3 (5%)	4 (6%)	3 (5%)
eGFR, mL/min per 1·73 m²	38·00 (26·33–48·33)	35·33 (26·00–45·33)	37·33 (31·33–50·33)	37·17 (27·67–45·67)
High-sensitivity CRP, mg/L	5·80 (3·25–9·85)	5·53 (3·50–9·25)	5·70 (3·45–8·10)	5·80 (3·65–8·90)
IL-6, pg/mL§	5·24 (3·60–7·62)	4·85 (3·06–8·28)	5·11 (3·79–9·44)	6·63 (4·07–9·01)



Targeting IL-6 in anemia management

CLINICAL RESEARCH www.jasn.org OPEN

Effect of Ziltivekimab on Determinants of Hemoglobin in Patients with CKD Stage 3–5: An Analysis of a Randomized Trial (RESCUE)

Pablo E. Pergola,[1] Michael Davidson,[2] Camilla Jensen,[3] Amir A. Mohseni Zonoozi,[3] Dominic S. Raj,[4] Philip Andreas Schytz,[3] Katherine R. Tuttle,[5] and Vlado Perkovic[6]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background In the phase 2 RESCUE clinical trial, ziltivekimab, a fully human monoclonal antibody against the IL-6 ligand, significantly reduced the biomarkers of inflammation compared with placebo, in patients with CKD and systemic inflammation (high-sensitivity C-reactive protein ≥2 mg/L). The aim of this subanalysis of RESCUE trial data was to assess the effect of ziltivekimab on Hb and iron homeostasis in this patient population.

Methods This was an analysis of exploratory end points from the RESCUE trial (NCT03926117), which included 264 adults with CKD stage 3–5 and high-sensitivity C-reactive protein ≥2 mg/L. Participants received placebo or subcutaneous ziltivekimab (7.5, 15, or 30 mg) (1:1:1:1) once every 4 weeks, up to 24 weeks. End points for this analysis were changes in Hb and biomarkers of iron homeostasis from baseline to week 12.

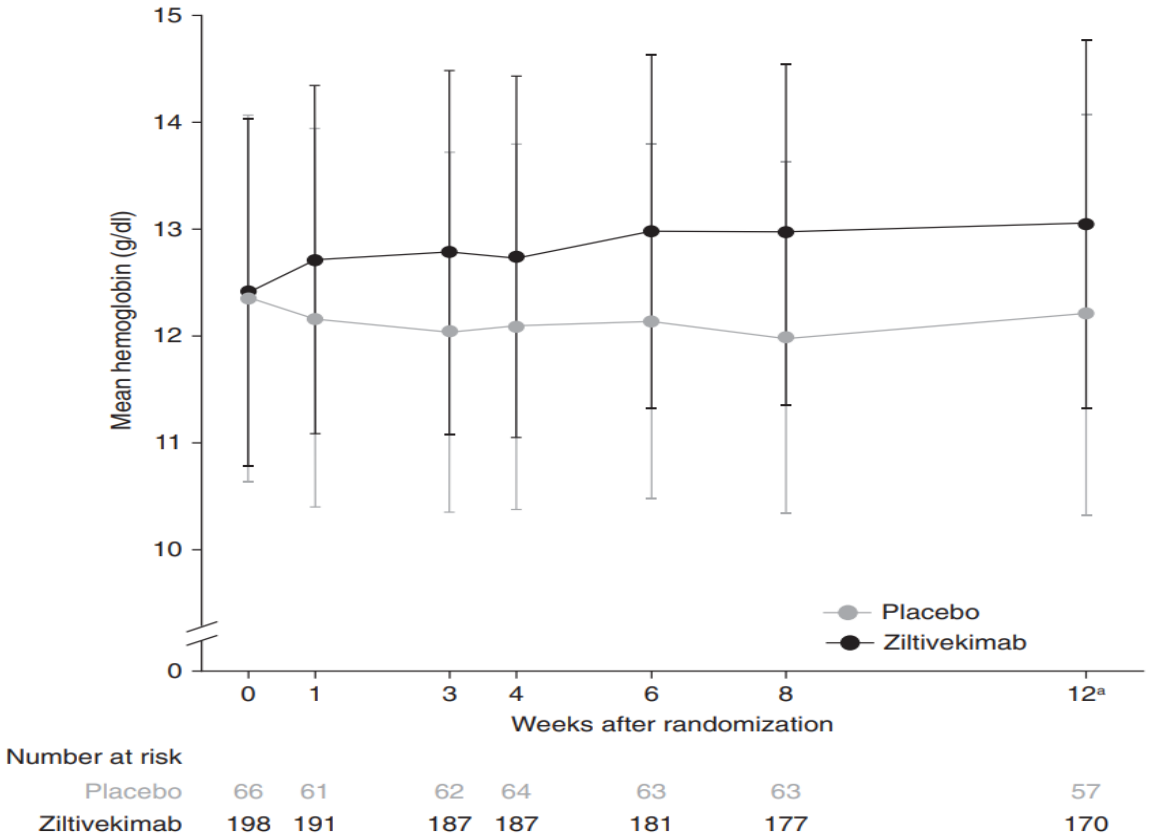


Table 2. Hb Levels at Baseline and at Week 12 and Estimated Change From Baseline and Treatment Difference

Hb Level	Placebo	Ziltivekimab 7.5 mg	Ziltivekimab 15 mg	Ziltivekimab 30 mg
Overall population				
Hb at baseline, mean (SD), g/dl	12.35 (1.71)	12.50 (1.63)	12.52 (1.70)	12.21 (1.55)
Hb at week 12, observed mean (SD), g/dl	12.20 (1.87)	12.67 (1.91)	13.39 (1.69)	13.05 (1.54)
Change from baseline to week 12, g/dl, estimated mean[a] (95% CI) [*n*]	−0.22 (−0.44 to −0.01) [*57*]	0.34 (0.12 to 0.56) [*53*]	0.82 (0.61 to 1.03) [*60*]	0.77 (0.55 to 0.99) [*57*]
Treatment difference[a] (95% CI), g/dl	—	0.57 (0.27 to 0.86)[c]	1.05 (0.76 to 1.33)[c]	0.99 (0.70 to 1.28)[c]
Baseline Hb <11 g/dl				
Hb at baseline, mean (SD), g/dl	9.92 (0.85)	10.23 (0.58)	10.54 (0.67)	10.05 (0.96)
Hb at week 12, observed mean (SD), g/dl	9.72 (1.32)	10.38 (0.86)	11.50 (1.01)	11.25 (1.13)
Change from baseline to week 12, g/dl, estimated mean[b] (95% CI) [*n*]	−0.29 (−0.75 to 0.17) [*12*]	0.07 (−0.38 to 0.51) [*13*]	0.80 (0.33 to 1.27) [*11*]	1.18 (0.71 to 1.66) [*11*]
Treatment difference[b] (95% CI), g/dl	—	0.36 (–0.26 to 0.98)	1.09 (0.45 to 1.73)[c]	1.48 (0.83 to 2.12)[c]
Baseline Hb ≥11 g/dl				
Hb at baseline, mean (SD), g/dl	12.94 (1.29)	13.05 (1.28)	13.05 (1.48)	12.79 (1.09)
Hb at week 12, observed mean (SD), g/dl	12.86 (1.37)	13.42 (1.52)	13.82 (1.51)	13.48 (1.29)
Change from baseline to week 12, g/dl, mean (95% CI)[b] [*n*]	−0.22 (−0.45 to 0.01) [*45*]	0.41 (0.16 to 0.65) [*40*]	0.81 (0.58 to 1.04) [*49*]	0.65 (0.42 to 0.89) [*46*]
Treatment difference[b] (95% CI), g/dl	—	0.62 (0.29 to 0.96)[c]	1.03 (0.71 to 1.35)[c]	0.87 (0.55 to 1.20)[c]

Table 3. Change From Baseline to Week 12 for Additional Biomarkers of Anemia

Biomarker	Outcome	Placebo	Ziltivekimab 7.5 mg	Ziltivekimab 15 mg	Ziltivekimab 30 mg
Ferritin	Change from baseline to week 12 μg/L, estimated mean[a] (95% CI) [*n*]	–16.56 (–45.10 to 11.97) [*57*]	–23.77 (–52.59 to 5.04) [*58*]	–7.13 (–35.44 to 21.18) [*61*]	–22.38 (–51.74 to 6.99) [*57*]
	Treatment difference[a] (95% CI), μg/L	—	–7.21 (–43.61 to 29.18)	9.43 (–26.70 to 45.56)	–5.81 (–42.65 to 31.02)
Hepcidin	Change from baseline to week 12, μg/L, estimated mean[a] (95% CI) [*n*]	–3.85 (–16.63 to 8.93) [*56*]	–13.49 (–26.48 to –0.49) [*57*]	–15.50 (–28.21 to –2.78) [*60*]	–18.79 (–31.98 to –5.61) [*56*]
	Treatment difference[a] (95% CI), μg/L	—	–9.64 (–25.97 to 6.69)	–11.65 (–27.84 to 4.55)	–14.94 (–31.45 to 1.56)
Iron	Change from baseline to week 12, μg/dl, estimated mean[a] (95% CI) [*n*]	–1.91 (–10.94 to 7.13) [*57*]	16.34 (7.24 to 25.43) [*58*]	28.82 (19.84 to 37.81) [*61*]	32.89 (23.61 to 42.17) [*57*]
	Treatment difference[a] (95% CI), μg/dl	—	18.24 (6.75 to 29.74)[c]	30.73 (19.33 to 42.13)[d]	34.79 (23.18 to 46.40)[d]
TIBC	Change from baseline to week 12, μg/dl, estimated mean[a] (95% CI) [*n*]	–0.04 (–8.04 to 7.96) [*56*]	14.23 (6.21 to 22.25) [*58*]	17.72 (9.86 to 25.59) [*61*]	24.36 (16.20 to 32.51) [*57*]
	Treatment difference[a] (95% CI), μg/dl	—	14.27 (4.09 to 24.44)[c]	17.76 (7.68 to 27.84)[d]	24.39 (14.12 to 34.66)[d]
Transferrin saturation	Change from baseline to week 12, %, estimated mean[a] (95% CI) [*n*]	–0.26 (–2.80 to 2.27) [*57*]	3.77 (1.21 to 6.32) [*58*]	7.05 (4.53 to 9.57) [*61*]	7.69 (5.08 to 10.30) [*57*]
	Treatment difference[a] (95% CI), %	—	4.03 (0.80 to 7.27)[b]	7.31 (4.12 to 10.51)[d]	7.95 (4.70 to 11.21)[d]

Other therapeutic options : Hepcidin Antagonists

❖ Direct Hepcidin Blockade: **Lexaptepid (NOX-H94)**

➔ In healthy volunteer, single and multiple IV doses showed dose-dependent increases in serum iron, ferritin, and TSAT.

Br J Pharmacol. 2016;173:1580–8.

❖ Indirect Hepcidin Blockade: **Targeting Ferroportin and BMP6**

1) LY2928057 (anti-ferroportin monoclonal antibody)

➔ Concern: paradoxical risk of undesirable rise in serum hepcidin

2) LY3113593 (anti-BMP6 monoclonal antibody)

➔ In healthy volunteers: Increased serum iron and TSAT, and decreased hepcidin levels, but less effective

Br J Pharmacol. 2019;85:935–48

Brief Report

CLINICAL TRIALS AND OBSERVATIONS

Effect of the antihepcidin Spiegelmer lexaptepid on inflammation-induced decrease in serum iron in humans

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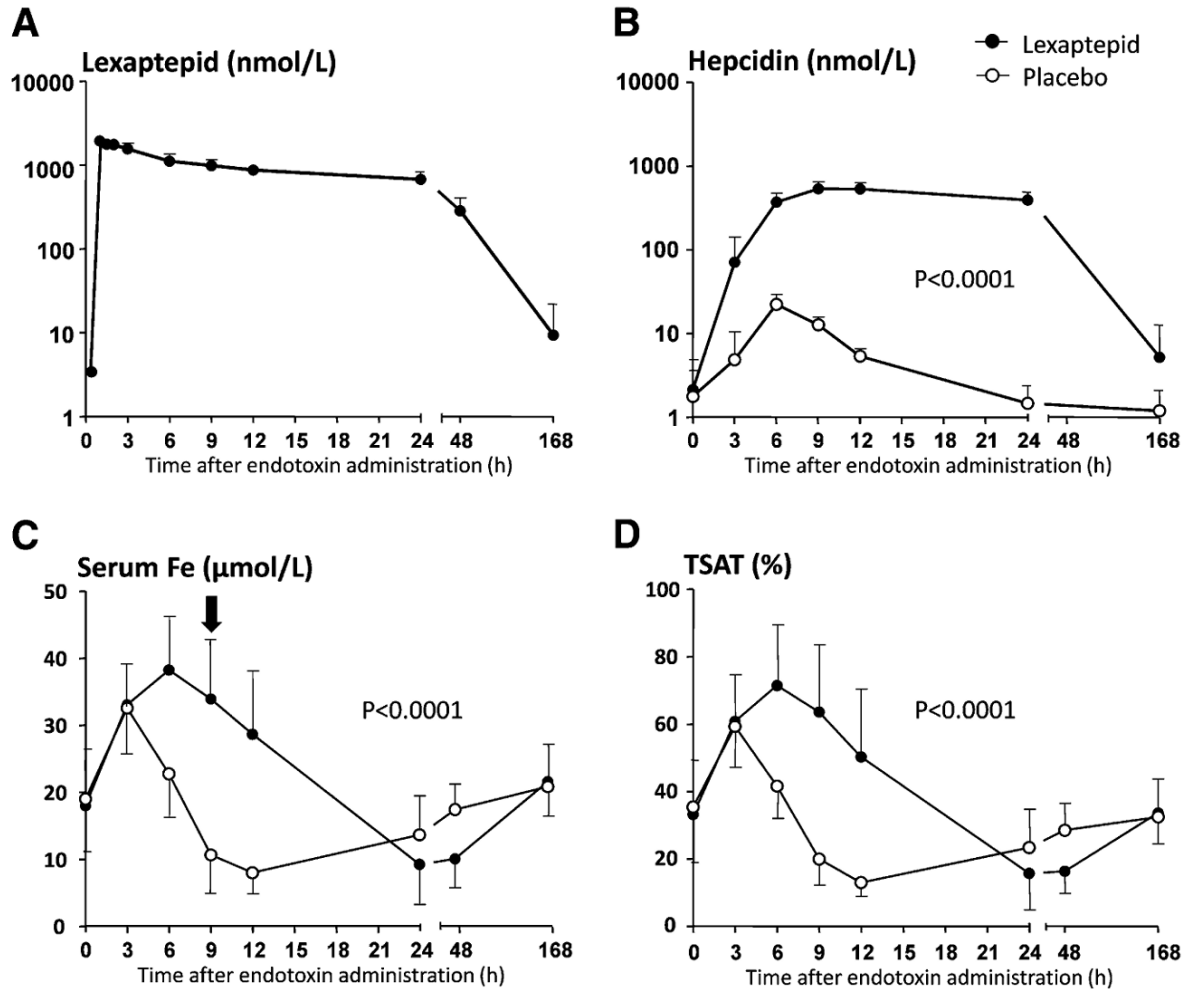
Key Points

- Lexaptepid modulates the inflammation-induced decrease in serum iron during experimental human endotoxemia.
- Hepcidin targeting with the novel compound lexaptepid may be a viable approach to the treatment of anemia of inflammation in humans.

Increased hepcidin production is key to the development of anemia of inflammation. We investigated whether lexaptepid, an antihepcidin L-oligoribonucleotide, prevents the decrease in serum iron during experimental human endotoxemia. This randomized, double-blind, placebo-controlled trial was carried out in 24 healthy males. At T = 0 hours, 2 ng/kg *Escherichia coli* lipopolysaccharide was intravenously administered, followed by an intravenous injection of 1.2 mg/kg lexaptepid or placebo at T = 0.5 hours. The lipopolysaccharide-induced inflammatory response was similar in subjects treated with lexaptepid or placebo regarding clinical and biochemical parameters. At T = 9 hours, serum iron had increased by 15.9 ± 9.8 μmol/L from baseline in lexaptepid-treated subjects compared with a decrease of 8.3 ± 9.0 μmol/L in controls ($P < .0001$). This study delivers proof of concept that lexaptepid achieves clinically relevant hepcidin inhibition enabling investigations in the treatment of anemia of inflammation. This trial was registered at www.clinicaltrial.gov as #NCT01522794. (*Blood*. 2014;124(17):2643-2646)



Take home messages

❖ **ESA hyporesponsiveness**

Screen for factors

- **Clinical assessment**
- **Serum investigations** i.e. iron studies, infection/inflammatory markers, renal function
- **Multidisciplinary Team assessment** i.e. Nephrologist, Dieticians, Physiotherapy

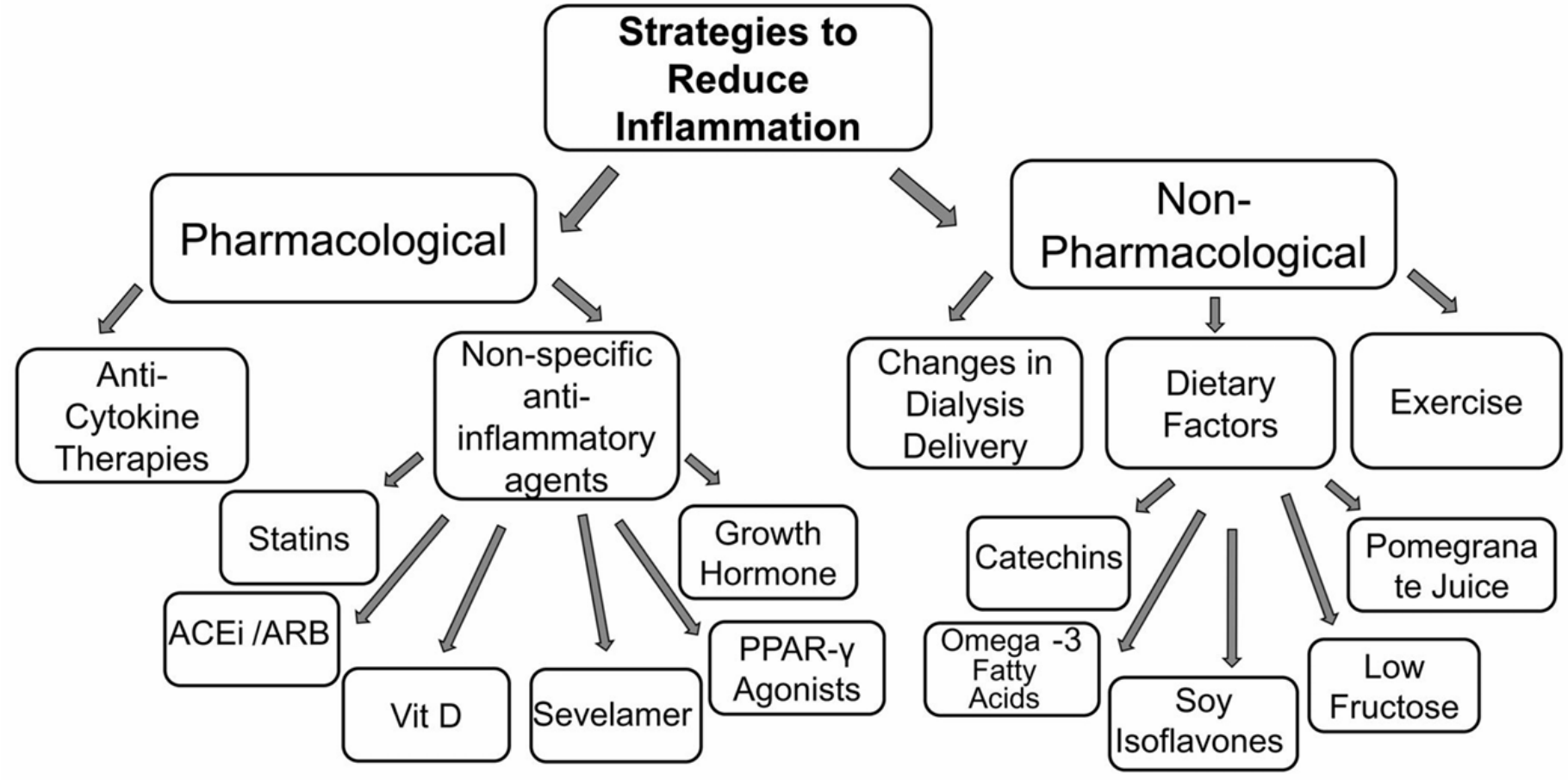
Address Factors

- Oral/IV Iron
- Treat underlying source of infection and inflammation
- Improve dialysis delivery
- Non-iron Nutritional Supplement
- Regular monitoring in primary & secondary care
- Multidisciplinary Team Involvement

Consider HIF-stabilizers

- Multidisciplinary clinical assessment deem overall benefits outweigh risks
- Low Carcinogenic Risks
- Satisfactory cardiorespiratory function
- Patient Preference

Take home messages



非常感謝大家的聆聽

Thank you very much for listening

감사합니다

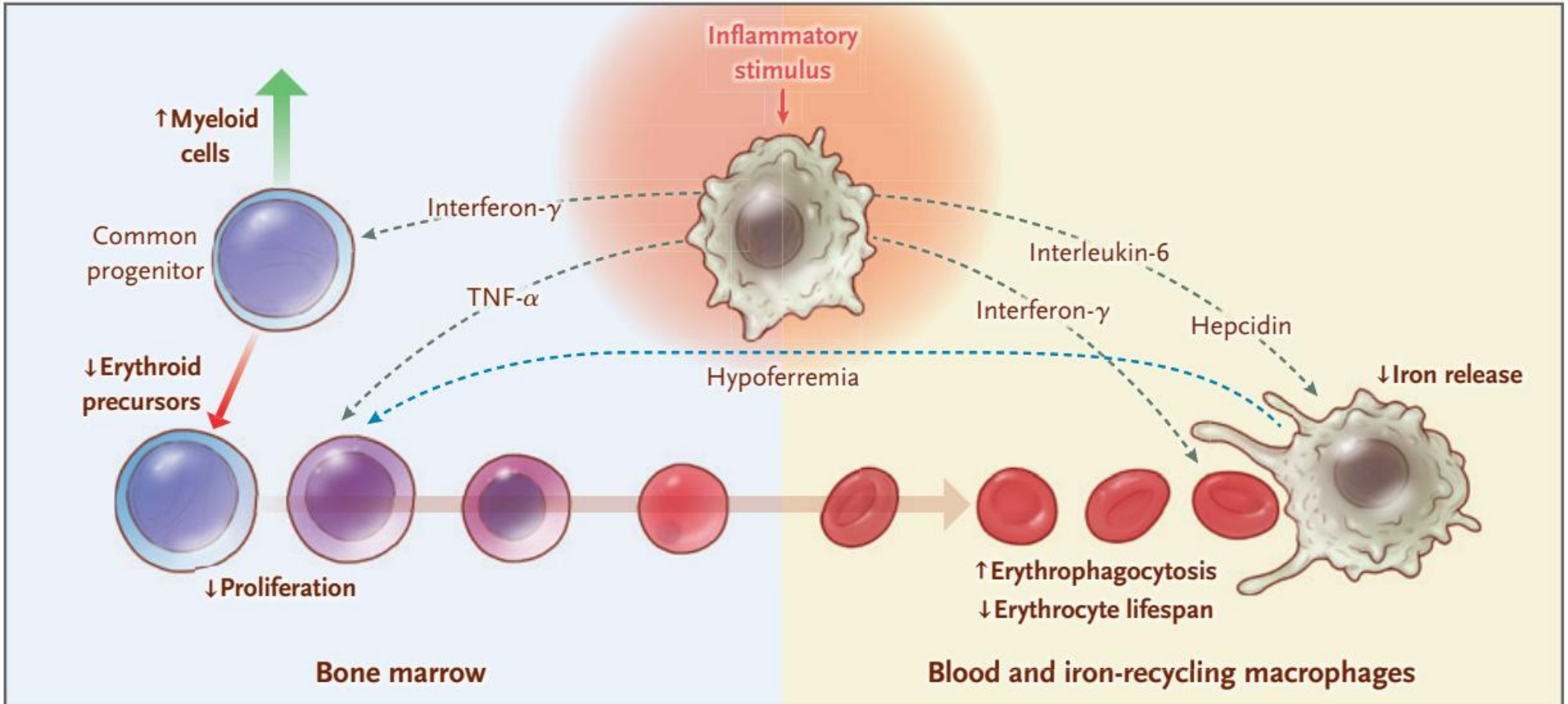


Figure 2. Role of Systemic Inflammation in Anemia.

Systemic inflammation is characterized by high levels of cytokines that bias hematopoiesis toward myeloid-cell production (large green arrow) rather than erythropoiesis (red arrow) (interferon-γ), inhibit erythroid-precursor proliferation (tumor necrosis factor α [TNF-α]), activate macrophages for erythrophagocytosis and thereby shorten the erythrocyte lifespan (interferon-γ), and inhibit the release of recycled iron from macrophages (interleukin-6 through hepcidin), causing hypoferremia. Hypoferremia inhibits erythroblast proliferation. The dashed lines represent soluble mediators that regulate erythropoiesis during inflammation.