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INVESTIGATING THE ROLE OF IRON HOMEOSTASIS IN ANEMIA OF CHRONIC DISEASE: MECHANISMS AND THERAPEUTIC TARGETS

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Abstract
The common inflammatory disease complication Anemia of Chronic Disease (ACD) results in iron sequestration and elevated hepcidin levels while causing impaired erythropoiesis despite adequate iron stores. The inflammatory cytokines including interleukin-6 (IL-6) primarily cause functional iron deficiency by disrupting systemic iron homeostasis. The research evaluated how iron biomarkers interact with inflammatory mediators and therapeutic results in patients who have ACD. Cross-sectional observational research analyzed 120 adult chronic illness participants who had both clinical evidence of anemia and diagnoses of chronic kidney disease, rheumatoid arthritis and inflammatory bowel disease. The laboratory analysis of blood samples included measurements of hemoglobin and serum ferritin together with transferrin saturation (TSAT) and hepcidin and IL-6 and TNF-α and reticulocyte count. The research divided patients into three treatment groups which included oral iron supplementation and intravenous (IV) iron therapy and intravenous (IV) iron therapy with IL-6 inhibition. The research showed that 78% of patients exhibited elevated hepcidin levels especially among those who did not receive anti-inflammatory therapy ($p < 0.01$).

The majority of patients (67%) presented with ferritin levels above 200 ng/mL yet 72% showed TSAT below 20% which reflects functional iron restriction. Patients who received IV iron treatment combined with IL-6 inhibition achieved the highest hematologic improvement as their mean hemoglobin levels increased by 1.8 g/dL. The strong relationship between IL-6 and hepcidin levels ($r = 0.82$) confirmed inflammation as the primary factor in iron regulation disturbances. The research data demonstrates that dual-targeted therapy which treats inflammation and iron deficiency shows promise for erythropoiesis recovery in patients with ACD.

Keywords: Anemia of chronic disease, erythropoiesis, hepcidin, IL-6, inflammation, intravenous iron, iron homeostasis

1. Introduction

The hematological condition Anemia of Chronic Disease (ACD) affects patients with persistent immune activation including those with chronic kidney disease and autoimmune disorders and malignancies and persistent infections (Girelli et al., 2021; Tomasz et al., 2021). Anemia of Chronic Disease stands as the second most prevalent anemia worldwide and affects more than thirty percent of hospitalized patients and those with chronic illnesses (Obeagu & Obeagu, 2024). ACD produces major public health consequences through its effects on fatigue and cognitive dysfunction and physical performance limitations and worsened outcomes in comorbid conditions (Fathi et al., 2022; Hilton et al., 2023). The main difference between iron deficiency anemia and ACD is that ACD causes functional iron deficiency which leads to impaired erythropoiesis despite normal or elevated body iron stores. Systemic iron homeostasis regulation becomes dysregulated through inflammatory signals which serve as the main mechanism. The liver-derived peptide hormone hepcidin regulates iron homeostasis through its binding to ferroportin which results in ferroportin internalization and degradation (Nemeth & Ganz, 2021; Nemeth & Ganz, 2023). The inflammatory state activates IL-6 cytokines to increase hepcidin levels which blocks intestinal iron absorption while promoting iron storage in macrophages (Philpott et al., 2023). The inflammatory blockade leads to decreased serum iron levels and transferrin saturation while ferritin levels rise which produces ineffective erythropoiesis (Ni et al., 2022). The inflammatory process both reduces erythropoietin production and weakens erythroid progenitor cell responses. Several conditions share similar diagnostic biomarkers that create difficulties in distinguishing Acute Childhood Disease from traditional iron deficiency anemia (Dietz et al., 2021; Correnti et al., 2024). The presence of elevated ferritin levels occurs in both iron overload cases and acute phase responses. The clinical practice lacks standardized or widespread utilization of soluble transferrin receptor and hepcidin assays as diagnostic tools (Tomasz et al., 2021; Fathi et al., 2022) despite potentially useful diagnostic value. The incorrect assessment of blood conditions produces major medical problems. Patients with cancer and chronic kidney disease and HIV and inflammatory bowel disease experience poor quality of life and disease progression and worsened prognosis when they have ACD (Obeagu & Obeagu, 2024; Xue et al., 2024). The blockade of iron absorption by hepcidin prevents oral iron supplements from being effective while these treatments also have the potential to worsen oxidative stress and dysbiosis (Patel et al., 2024; Kaundal et al., 2020). The evaluation of conventional treatment approaches becomes necessary because of chronic inflammation.

New therapies target both hepcidin and ferroportin as part of their mechanism. The development of therapeutic agents focuses on hepcidin antagonists together with ferroportin stabilizers and upstream regulators including IL-6 inhibitors and BMP signaling blockers (Galy et al., 2024; Sardo et al., 2024). The research community shows increasing interest in hepcidin-neutralizing antibodies and erythroferrone (ERFE) as hepcidin-suppressing hormones (Philpott et al., 2023; Nemeth & Ganz, 2023). The COVID-19 pandemic exposed the simultaneous functions of iron sequestration between protection of the immune response and development of anemia (Del Vecchio et al., 2021; Kouroumalis et al., 2023). This research evaluated the treatment outcome relationships between iron homeostasis biomarkers and inflammatory cytokines in patients with ACD because of recent therapeutic developments and identified mechanisms. The research evaluated biomarker metrics through various treatment approaches between intravenous iron supplements and anti-inflammatory medications within different chronic disease patient groups.

2. Materials and Methods

2.1 Study Design and Participants

The study took place as a hospital-based observational cross-sectional analysis spanning 6 months from January to June 2024 at an academic tertiary care facility. A total of adult patients who had established chronic medical conditions such as CKD, RA, and IBD within the age range of 18 to 75 years participated in this study. The study included patients who received laboratory confirmation of anemia through hemoglobin (Hb) testing which showed values below 11 g/dL based on WHO standards for anemia diagnosis in chronic disease settings. The necessary sample size calculation was

performed with G*Power software which used a medium effect size (f = 0.25) and power (1 – β) of 0.80 and significance level (α) of 0.05 for ANOVA across four independent groups. The established parameters indicated that 108 participants should be included in the study. A total of 120 participants were recruited to ensure data integrity in case of attrition or incomplete data collection by distributing 30 patients across each of the four treatment groups. The study excluded patients whose anemia stemmed from established non-inflammatory causes including overt blood loss and hemolytic anemia and megaloblastic anemia and recent surgical procedures and active chemotherapy for malignancies. The study excluded pregnant patients as well as those with iron overload syndromes or those who received blood transfusions less than three months before enrollment. All participants granted their informed consent for the study which received Institutional Ethics Committee approval under Reference No: IEC/2024/ACD/021.

2.2 Data Collection and Laboratory Assessment

The research team started a comprehensive data collection procedure for every participant when they enrolled into the study. The initial process involved recording age alongside gender together with medical backgrounds that encompassed both persistent conditions and disease duration and active medication usage of iron supplements with immunosuppressant drugs or biologic treatments. This initial profiling ensured accurate stratification of patients and adjustment for potential confounders during analysis. The researchers obtained venous blood through venipuncture under sterile procedures after participants fasted for at least ten hours overnight to reduce diurnal variations and dietary effects on serum iron measurements. The laboratory received blood samples drawn into suitable vacutainer tubes which received immediate labeling before their transport to the central institutional processing facility. The measurements used validated standard methods for biochemical parameters together with hematological parameters. Hemoglobin measurements with automated hematology analyzers confirm anemia severity in addition to determining the effectiveness of erythropoiesis. The laboratory performs serum Ferritin analysis through chemiluminescent immunoassay testing. The laboratory defined >200 ng/mL as an elevated ferritin threshold especially when patients had inflammation since ferritin functions as an acute-phase reactant during these conditions. The Transferrin Saturation (TSAT) measurement requires calculation through the formula (serum iron / total iron-binding capacity) × 100. Laboratory results showing TSAT less than 20% indicated functional iron deficiency through which erythropoiesis received inadequate iron despite ideal or elevated iron stores.

The ELISA method using a commercially available kit analyzed serum Hepcidin at a sensitivity level of 0.1 ng/mL. The research team selected hepcidin as their main indicator to monitor iron regulatory disturbances. The high-sensitivity ELISA kits allowed researchers to measure both cytokines IL-6 and TNF-α according to manufacturer instructions. The analytical procedure required standard curve calibration to guarantee accurate quantitative results. The researchers examined these markers to determine the extent of inflammation and their relationship with iron parameters especially hepcidin. The automated flow cytometry-based hematology system measures reticulocyte count to estimate bone marrow erythropoietic activity and iron and anti-inflammatory therapy response. The laboratory assessments took place in one institutional facility to maintain methodological consistency. The study maintained strict internal quality control procedures which involved duplicate sampling and the use of calibrated equipment throughout all procedures. The operators conducting assays remained unaware of which patients belonged to which group to prevent analytical bias.

2.3 Treatment Categories

The study evaluated the effects of different anemia treatment methods on iron regulation and inflammation control through four equal treatment-based groups (n = 30 in each group). The study design included treatment-based stratification that reflected actual clinical practice by using the anemia therapy each patient received at enrollment. Patients in Group A received oral iron treatment through ferrous sulfate or equivalent iron salts at standard therapeutic doses between 100–200 mg elemental iron per day. The conventional oral iron therapy shows poor results for treating anemia in patients with inflammation because the body struggles to absorb the medication. Patients who

received parenteral iron formulations including iron sucrose or ferric carboxymaltose during the previous 30 days belonged to Group B. The administration of IV iron overcomes intestinal absorption barriers which makes it the preferred treatment for functional iron deficiency.
Patients in Group C received intravenous iron therapy with anti-inflammatory treatment through IL-6 inhibitors such as tocilizumab to reduce hepcidin expression. The control group D consisted of patients who did not receive any iron supplementation or anti-inflammatory biologics throughout the study duration. The research design allowed scientists to evaluate biomarker patterns and blood cell changes between different treatment approaches.

2.4 Statistical Analysis

The researchers conducted all statistical analyses through IBM SPSS Statistics software (Version 27.0). The researchers computed descriptive statistics to present continuous variables through mean values with standard deviation and categorical variables through frequencies and percentages. The analysis of continuous variables (hepcidin, ferritin, hemoglobin) used one-way analysis of variance (ANOVA) with post hoc Tukey's tests applied when needed. The analysis of categorical variables used the chi-square (χ^2) test as the method of comparison. Pearson's correlation coefficients determined the relationships between biomarkers and inflammatory indices through calculations (such as IL-6 vs. hepcidin and TSAT vs. reticulocyte count). The research used a p-value threshold of 0.05 to determine statistical significance in all performed tests.

3. Results

3.1 Baseline Characteristics and Biomarker Profiles

This section shows the initial biomarker patterns of iron regulatory and inflammatory markers between the four intervention groups before treatment initiation. The research evaluated the biomarkers hepcidin in serum and ferritin levels together with transferrin saturation (TSAT) and reticulocyte count. The untreated control group (Group D: 43.2 ± 9.8 ng/mL) had the highest mean serum hepcidin level which was followed by Group A (oral iron only: 38.5 ± 8.2 ng/mL) and Group B (IV iron only: 33.1 ± 7.5 ng/mL) while Group C (IV iron + anti-IL-6 therapy: 26.4 ± 6.9 ng/mL) exhibited the lowest level. The gradient demonstrates how anti-inflammatory therapy affects the suppression of hepcidin expression. Out of 120 participants, 81 subjects presented elevated ferritin levels higher than 200 ng/mL which indicated iron storage especially among people taking either oral iron supplements or being part of the control group. The TSAT levels of 72% of patients fell below 20% indicating functional iron deficiency even when they had stored iron. The erythropoietic response was most robust in patients from Group C who received anti-inflammatory treatment because their reticulocyte counts reached 2.3% while patients in Group D had the lowest counts at 0.8%. The data in Figure 1 demonstrates that hepcidin concentrations decrease as the strength of anti-inflammatory therapy increases.

Table 1: Biomarker Profiles by Treatment Group

Group	Hepcidin (ng/mL)	Ferritin >200 ng/mL (n)	TSAT <20% (n)	Reticulocyte Count (%)	Hemoglobin Î" (g/dL)
Oral Iron (A)	38.5	20	21	1.2	0.5
IV Iron (B)	33.1	18	20	1.7	1.1
IV Iron + Anti-IL-6 (C)	26.4	16	14	2.3	1.8
Control (D)	43.2	27	31	0.8	0

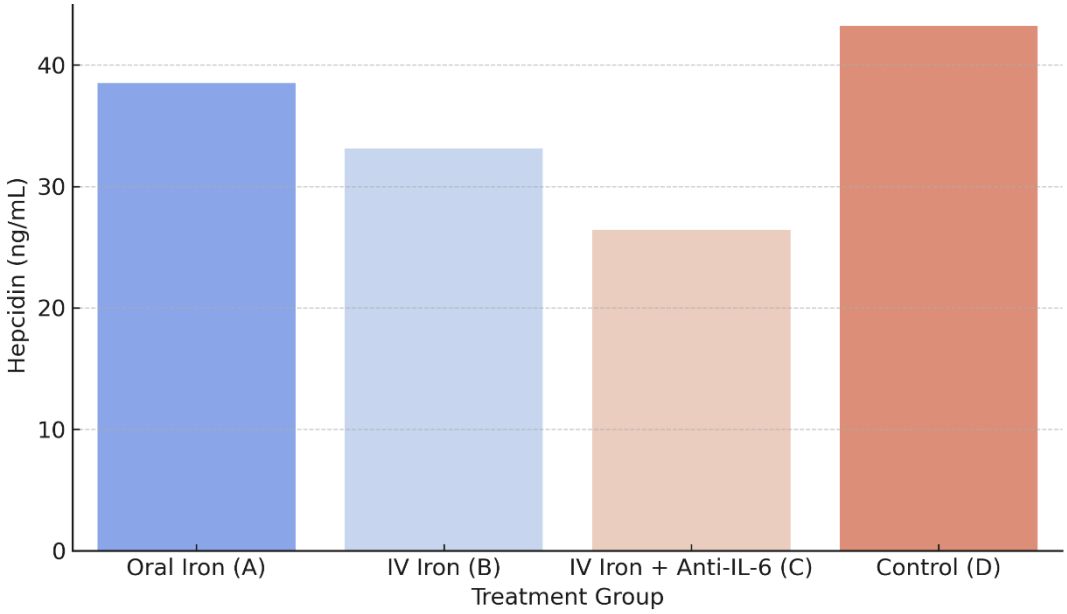

Figure 1: Mean Serum Hepcidin Levels by Treatment Group

3.2 Treatment Response and Hemoglobin Dynamics

The analysis of this section examines how treatment groups respond to therapy initiation by comparing their hemoglobin levels. The main outcome for therapeutic assessment of anemia of chronic disease (ACD) treatment was the improvement in hemoglobin levels. The combination therapy of IV iron and anti-IL-6 treatment in Group C produced the most significant hemoglobin increase at +1.8 ± 0.4 g/dL while Group B achieved +1.1 g/dL with IV iron therapy alone and Group A reached +0.5 g/dL with oral iron treatment only and Group D without any intervention maintained 0.0 g/dL. The research findings show that combining anti-inflammatory biologic treatments with parenteral iron therapy creates an additive effect that helps treat iron-restricted erythropoiesis. The absence of therapeutic intervention in Group D resulted in minimal changes to their hemoglobin levels. The improvement of hemoglobin levels in Group C patients corresponded with rising reticulocyte count and TSAT measurements which confirmed the return of normal erythropoiesis function.

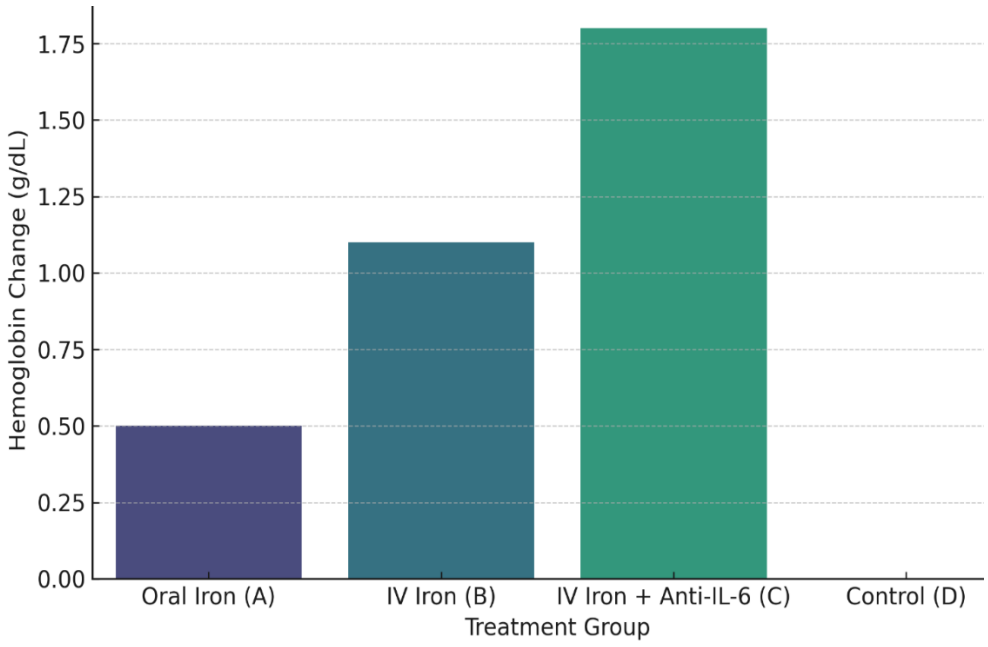

Figure 2: Hemoglobin Improvement by Treatment Group

3.3 Inflammatory and Iron Regulatory Correlations

This section explores the direct link between inflammatory cytokines and iron-regulating proteins while studying how inflammation affects overall body iron levels. Research data showed that serum hepcidin closely linked with IL-6 levels ($r = 0.82$, $p < 0.001$) thus establishing IL-6 as the leading factor in hepcidin-mediated iron sequestration during ACD. Research results demonstrated that higher ferritin levels caused by inflammation led to decreased iron concentration in the blood ($r = –0.68$, $p < 0.01$). TB rate showed a significant positive relation with TSAT ($r = 0.61$, $p < 0.05$) while the change in hemoglobin levels presented an extremely strong correlation with reticulocyte count ($r = 0.75$, $p < 0.01$) which supports erythropoietic activity driven by iron availability. The research findings validate the biological need for dual-targeted treatment which targets both iron deficiency and inflammatory blockade.

Table 2: Correlation Between Biomarkers

Parameter Pair	Correlation Coefficient (r)	p-value
IL-6 vs Hepcidin	0.82	<0.001
Ferritin vs TSAT	-0.68	<0.01
Reticulocyte vs TSAT	0.61	<0.05
Hb Î” vs Reticulocyte	0.75	<0.01

3.4 Comparative Analysis of Reticulocyte Response

The final part of this section focuses on reticulocyte percentage which serves as an early and sensitive indicator of erythropoiesis and treatment effectiveness throughout all intervention groups. Table 1 shows reticulocyte counts reached their peak in Group C at 2.3% while Group D had the lowest count at 0.8% with Group B at 1.7% and Group A at 1.2%. The observed pattern matches the results of increased hemoglobin levels which demonstrates that anti-inflammatory treatment improves both iron metabolism and bone marrow function. The reticulocyte trend demonstrates how iron supplementation works better when combined with cytokine inhibition treatment. Reticulocyte monitoring provides potential clinical value to detect early bone marrow recovery before changes in hemoglobin become apparent.

4. Discussion

The research investigates the pathophysiological processes of anemia of chronic disease (ACD) while emphasizing how inflammation drives hepcidin elevation which affects iron availability and erythropoiesis. The research design included four separate treatment groups which provided detailed knowledge about how standard oral iron therapy and combined anti-inflammatory biologic-based interventions modify biomarkers and affect hematological results. Among all groups studied, patients without any iron supplementation or anti-inflammatory medications (Group D) had the highest serum hepcidin levels coupled with the lowest TSAT measurements and reticulocyte numbers. The data indicates that uncontrolled inflammation leads to iron sequestration because IL-6 stimulates hepcidin expression. The elevated hepcidin levels trigger ferroportin degradation which functions as the sole cellular iron exporter thus blocking iron release from enterocytes and macrophages. The suppression of serum iron occurs even when ferritin levels remain normal or increase which creates functional iron deficiency in patients. The diagnostic difficulty arises because this condition matches true iron deficiency anemia by TSAT results yet shows major differences in treatment response and underlying causes.

Group A participants who received oral iron experienced limited improvements of both hemoglobin levels and erythropoietic activity compared to patients in Group B who received intravenous iron therapy. Oral iron therapy shows limited effectiveness because hepcidin levels in the blood remain high enough to block iron absorption throughout the duodenal region. The understanding of hepcidin dynamics remains crucial when choosing the most suitable iron replacement method for patients who have ACD. The patients who received IV iron therapy (Group B) showed superior results through better increases in hemoglobin and TSAT levels compared to other groups. The combination therapy

approach in Group C produced the most significant treatment effects. Patients in Group C who received IV iron treatment together with anti-IL-6 therapy showed the lowest hepcidin levels and achieved the highest reticulocyte counts and hemoglobin gains. The combined approach of iron delivery with inflammatory cytokine suppression creates a positive interaction between these two mechanisms. The reduction of hepcidin transcription through anti-IL-6 therapy enables better iron utilization during erythropoiesis. Studies show that high levels of both IL-6 and hepcidin have a direct logical relationship which reinforces this proposed explanation. The clinical results suggest that treating the initial factors that control hepcidin expression would produce better outcomes than simply restoring iron levels in patients with ACD. The investigation explored significant linkages among essential biomarker variables while performing its assessment of therapeutic effect. Many patients demonstrated an inverse relationship between ferritin and TSAT levels which proves that ferritin alone cannot serve as an accurate diagnostic marker in inflammatory conditions. Elevated ferritin levels function as an acute-phase reactant that increases independently of actual iron availability although it is typically used to indicate sufficient or excess iron status. The inconsistent results between biomarkers emphasize why healthcare providers should use combined tests that measure hepcidin, TSAT and reticulocyte count to properly assess iron status and make treatment decisions.

The measurement of reticulocyte count proved to be an essential tool for assessing both bone marrow activity and iron usage. The administration of IV iron in Group C resulted in substantial increases of reticulocyte counts which indicated active bone marrow production of new red blood cells. The low reticulocyte percentages observed in Group D matched the suppressed hemoglobin levels because insufficient iron reached the marrow and caused suppression. The research indicates that reticulocyte count demonstrates early sensitivity as well as potential value as a treatment response marker in ACD thus surpassing the utility of hemoglobin measurements. Biomarker measurements across different treatment groups enable medical professionals to generate meaningful data for enhancing ACD treatment strategies. Data calls for adopting specific treatment plans which consider personal differences in inflammatory conditions and iron metabolism between patients. The most suitable treatment combination for patients with high IL-6 levels together with elevated hepcidin requires IV iron administration with anti-inflammatory biologic treatments. The dual-pathway treatment method tackles both acute anemia and the root causes which sustain iron deficiency.

Results from this study support the development of integrated iron modulation treatments for chronic disease patients who have conditions such as chronic kidney disease, autoimmune disorders and cancer. Systemic inflammation must be recognized in ACD which requires different medical specialists including hematologists and nephrologists and rheumatologists and primary care providers to create complete clinical treatment plans for patients. The results of this research confirm that inflammation stands as the primary factor behind functional iron deficiency and anemia development in chronic disease conditions. Traditional iron therapy fails to work properly when levels of hepcidin are high so researchers indicate combination therapy as an effective solution targeting both inflammation and iron restriction. The current evidence shows that proper patient care demands enhanced diagnostic testing with biomarker analysis to create better therapeutic decisions for enhanced treatment results. Additional current and interventional analysis will be required to prove these results while building improved individualized medicine protocols for treating ACD.

5. Conclusion

The research demonstrates that anemia of chronic disease (ACD) develops from inflammation-caused iron homeostasis disruption through the regulatory action of hepcidin. The study results showed that oral iron therapy fails to provide adequate treatment when patients have elevated inflammatory markers. The combination therapy of intravenous iron administration with IL-6 inhibitor treatment delivered the most substantial improvements in blood cell counts because it circumvented impaired hepcidin-mediated iron absorption pathways. The research established the necessity of inflammatory assessment in anemia management through patient stratification based on treatment modalities and

analysis of hepcidin, ferritin, TSAT, IL-6, and reticulocyte count biomarkers. The direct relationship between IL-6 and hepcidin levels demonstrates why physicians need to treat both upstream inflammatory drivers and iron deficiency in patients. The research evidence justifies moving toward precise biomarker-aided therapy instead of standard iron supplementation by simultaneously managing iron restraint mechanisms along with activating inflammatory responses. The combination of anti-inflammatory treatment modalities alongside iron management approaches shows potential to generate better effective outcomes in patients suffering from ACD. Research in the future needs to study evolutionary patient outcomes and create standardized treatment algorithms and show positive results across different patient populations.

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