



Research Article

Hepcidin Modulators: A Potential Alternative Treatment of Iron Deficiency and Iron Deficiency Anemia in Heart Failure

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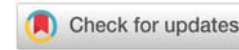
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Abstract

Heart failure affects roughly 6.7 million Americans and is associated with many comorbidities and complications, including iron deficiency and anemia. Iron homeostasis is integral to optimal body function. Hepcidin, a hepatically produced peptide, is a major modulator in iron homeostasis. Its synthesis is induced in part by inflammatory states. Iron deficiency in heart failure is currently diagnosed with the assessment of serum ferritin and percent of transferrin saturation. Iron deficiency in the setting of hepcidin excess in inflammatory conditions, such as heart failure, is discussed in this literature review. Iron deficiency is associated with worse prognosis and poorer outcomes in heart failure patients. Targeted treatment of iron deficiency and iron deficiency anemia may provide improved quality of life and decrease mortality and morbidity among heart failure patients. Current treatment options for iron deficiency and anemia include intravenous and oral iron supplementation, as well as other erythropoiesis-stimulating agents. However, concerns regarding safety have been raised in regards to these options. An emerging possibility for the treatment of iron deficiency in the setting of hepcidin overload is hepcidin modulators, including hepcidin antagonists or inhibitors. This review has addressed iron deficiency and anemia in heart failure and suggests that hepcidin antagonists/inhibitors may provide a viable alternative to the classic treatment methods.

Introduction

Heart failure is characterized by ventricle structural and/or functional impairment that compromises ventricular filling (diastolic dysfunction) or blood ejection (systolic dysfunction) [1]. It is a leading cause of mortality and morbidity, currently affecting about 6.7 million Americans [2]. The aging population has an even higher prevalence [3]. The overall prevalence of Heart Failure (HF) is estimated at 1.9% - 2.6% [2]. HF is the most common cause of hospitalizations in patients \geq 65 years old [4]. Incidence and prevalence continue to rise in the United States [5] and lifetime risk is an estimated 24% [2].

Risk factors and common causes of HF include hypertension, obesity, prediabetes and diabetes, and atherosclerotic disease, of which an estimated 115 million, 100 million, 92 million, 26 million, and 125 million people suffer, respectively [3]. Other possible etiologies include previous chemotherapy treatment, rheumatologic or autoimmune disease, cardiomyopathy

and myocarditis, and substance use (alcohol, cocaine, and methamphetamine) [3].

HF is diagnosed based on a constellation of criteria and symptomology, including evident structural and/or functional changes in the heart with associated clinical presentation and evidence of increased Left Ventricular (LV) filling pressures. Echocardiography is utilized in the diagnosis of suspected HF as it provides an estimation of Left Ventricular Ejection Fraction (LVEF). LVEF is subsequently used in the categorization of HF [3]. The categories of HF are outlined in Table 1. B-Type Natriuretic Peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are biomarkers frequently utilized in diagnosing HF. Serum levels and their correlation with HF likelihood are outlined in Table 2, which has been adapted from Thygesen, et al. [6].

Additional initial laboratory evaluation recommended at the time of diagnosis includes Complete Blood Count (CBC),

**Table 1:** The categorization of heart failure is determined by LVEF.

Heart failure category	Left Ventricular Ejection Fraction (LVEF) measurement
Heart failure with preserved ejection fraction (HFpEF)	LVEF \geq 50% [3,5,8]
Heart failure with improved ejection fraction (HFimpEF)	A previous LVEF LVEF \leq 40% with improvement at follow-up of $>$ 40%.
Heart failure with mid-range ejection fraction (HFmrEF)	LVEF 41%-49% [1,3,7,5]
Heart failure with reduced ejection fraction (HFrEF)	LVEF \leq 40% [1,3]

Table 2: BNP and NT-proBNP as indications of HF diagnosis.

Biomarker	Serum level	Likely outcome
BNP	BNP $<$ 100 ng/L	Unlikely to have HF
	BNP $>$ 500 ng/L	Likely to have HF*
NT-proBNP	NT-proBNP $<$ 300 ng/L	Unlikely to have HF
	Age	Level
	$<$ 50 years old	NT-proBNP $>$ 450 ng/L
	50-75 years old	NT-proBNP $>$ 900 ng/L
	$>$ 75 years old	NT-proBNP $>$ 1800 ng/L

*Those with a likely outcome of HF have a diagnosis confirmed through echocardiography [6].

urinalysis (UA), serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, fasting lipid profile, liver function tests (LFTs), iron studies, and thyroid stimulating hormone (TSH) levels [3]. These laboratory studies are used to evaluate potential causes and assess the risk for comorbidities. They also provide information on potential treatment response and prognosis of HF [3]. These labs, as relevant, may be repeated throughout a patient's disease course in an effort to assess and accommodate changes in clinical presentation and monitor treatment responsiveness and prognosis [3].

The clinical course is primarily monitored with routine NT-proBNP and troponin. These biomarkers are preferred when predicting adverse outcomes [7]. Of note, natriuretic peptides (NPs) (e.g. B-type natriuretic peptides) are not specific to HF. Elevations have been noted in other pathologies including pericardial disease, atrial fibrillation, myocarditis, cardioversion, advancing age, anemia, renal failure, obstructive sleep apnea, severe pneumonia, bacterial sepsis, and severe burns, among many others [3].

The pathogenesis of HF is multifactorial. Proposed mechanisms include impaired hemodynamics, the cardiorenal relationship, neurohormonal input, calcium homeostasis dysfunction, and cell death [8]. Of interest in the current review is the role of inflammation and pro-inflammatory cytokines and mediators as it relates to ID and hepcidin regulation. Inflammation is widely accepted in the pathogenesis of HF [1,7,9-21].

The predominant inflammatory cytokines considered in the pathophysiology of HF are tumor necrosis factor- α (TNF- α), interleukin (IL)-1, IL-6, IL-1 β , angiotensin (ANG) II, myostatin, and IL-18 [13-15,22]. These cytokines, especially TNF- α and IL-6, have been implicated in perpetuating inflammation in HF [23] and they have been used to assess the prognosis of HF. Elevated serum levels have been associated with a worse functional class of HF as determined by the

New York Heart Association (NYHA) Functional Classification system [13,15,22]. The NYHA functional classification is based on subjective evaluation of a patient's functional capacity and activity tolerance. The classification provides a baseline to help guide treatment selection and show treatment efficacy [16].

Among those diagnosed with HF, comorbidities include diabetes mellitus, renal dysfunction and chronic kidney disease (CKD), iron deficiency (ID), anemia, hypertension, sleep disorders, pulmonary disease, mental health disorders, obesity, and substance use disorders [1,14]. Diabetes mellitus, CKD, and obesity have also been shown to cause chronic, low-grade inflammation in HF [14].

ID in HF is associated with worse outcomes due to decreased exercise performance and tolerance, increased risk of mortality, worsened prognosis, increased work of cardiac tissue, lower quality of life (QoL), and progression to anemia [24,25]. These implications, among others, of ID are important to consider when treating HF.

Iron deficiency in HF

37% of all systolic chronic HF (CHF) patients studied by Jankowska, et al. suffered from concomitant ID, while Parikh, et al. had a prevalence of 61%. Obesich, et al. had nearly all patients studied ($n = 148$) with anemia of chronic disease (ACD), also known as anemia of inflammation (AI) with an etiology of impaired iron supply [24].

ID is classified by labs as follows: serum ferritin $<$ 100 μ g/L OR transferrin saturation (TSAT) $<$ 20% OR serum ferritin 100 - 300 μ g/L AND TSAT $<$ 20% to confirm iron deficiency [9,15,24].

Two types of ID have been defined: absolute ID and functional ID. Absolute is characterized by an overall depletion of iron stores whereas functional is defined by either impaired metabolism and utilization of iron or insufficient supply to meet metabolic demands [15].

Iron homeostasis

Ideal iron homeostasis is a stable iron serum concentration of 10 - 30 μ M [9,17,26,27]. A total body iron content of 3 g - 4 g is normal for a healthy adult individual. Of these 3 g - 4 g, 1 mg - 2 mg is absorbed per day and 25 mg, which is primarily sequestered from iron recycling, is required for daily erythropoiesis [9,17,26,27]. Iron, which is absorbed from the diet, recycled by macrophages, or stored in hepatocytes, is exported via the iron transporter, ferroportin [26]. Iron homeostasis and regulation are primarily impacted by hepcidin.

Chronic alterations from this concentration goal result in disease and are implicated in impaired hemoglobin (Hb) synthesis and eventual anemia. Additionally, dysfunctional iron homeostasis causes impaired ferroprotein synthesis. Serum iron concentration fluctuations are involved in the pathogenesis of nail, tongue, and esophageal epithelial impairments, related to deficits in both cognitive ability and muscular performance and are a cause of alterations in adaptive immune responses [26,28].

Hepcidin function

The key to regulating systemic iron homeostasis in the body is the peptide hormone, hepcidin. Hepcidin is primarily produced by hepatocytes (systemic effects) [26]. Secondary producers of hepcidin include cardiomyocytes, dendritic cells, and keratinocytes (local paracrine and autocrine effects) [26]. Cardiomyocytes regulate iron homeostasis in the heart while dendritic cells and keratinocytes regulate iron homeostasis as it relates to infection and inflammation [26].

Hepcidin mechanism of action

Hepcidin negatively controls the flow of iron from the plasma fluid compartment by inhibiting the absorption and release of iron. Specifically, it inhibits iron efflux either by directly binding and occluding the iron transporter, ferroportin, or by inducing a conformational change in the ferroportin protein. As a result of the conformational change, ferroportin is ubiquitinated and marked for endocytosis for lysosomal destruction [26]. Consequently, excess hepcidin results in low serum levels of iron (hypoferremia) via cellular iron retention, limiting its use in metabolic processes and normal cellular functions [27].

Hepcidin regulation

Hepcidin is regulated by many avenues, including iron itself, erythropoiesis activity, pregnancy, and infectious and inflammatory disease states. Hepcidin release is suppressed under the conditions of deficient iron, active erythropoiesis, and pregnancy. The purpose of suppression during these systemic states is to provide ample iron for normal functioning as the body demands change. Hepcidin release is induced under abundant iron, inflammatory, and infectious states in an effort to retain iron inside cells for functional and metabolic use as demand changes [26].

Under inflammatory processes, hepcidin production is stimulated by IL-6 and other proinflammatory cytokines with the goal of retaining iron in macrophages to counteract the increase in iron recycling by damaged tissues [9,17,26]. Therefore, it is reasonable to suggest modulating hepcidin as a target in the treatment of ID during chronic and acute inflammatory processes.

It is the aim of this review to establish that for patients with a current diagnosis of heart failure with iron deficiency with or without iron deficiency anemia, treatment with hepcidin inhibitors or antagonists may offer an alternative to other treatments of iron deficiency.

Methods

To establish that hepcidin is connected to iron deficiency, the initial search criteria for the primary inquiry of this paper was (iron deficiency + hepcidin antagonists). These criteria were entered into the medical journal database, PubMed, providing a yield of 96 articles. Of these 96 articles, five were filtered out using an English language filter. Of the remaining 91, 18 were selected for review based on the title and abstract, as the remainder did not pertain to the principle aim of this

literature review. Of the 18 articles, one was filtered out as an English language version was ultimately unobtainable. One was excluded due to no direct correlation to the current research goals. Seven were excluded as a full article text was unobtainable (Figure 1).

For acquiring the full text for the nine articles reviewed, the full-text article link from PubMed was utilized. Five full-text articles were obtained via PubMed Central, one directly from The Journal of Hepatology, and three from Elsevier Full Text Article.

Original sources that were cited in the review articles were also reviewed and included as pertinent to the aim of this literature review. Full-text articles were obtained in a similar fashion to the nine as previously outlined.

Discussion

ID in HF

ID is a common comorbidity and complication in HF. ID affected nearly 40% of the population in a study by Jankowska, et al. ($n = 546$) [8]. Nanas, et al. [29] found that among those hospitalized with chronic HF, bone marrow biopsies discovered that 73% had ID. This same study theorized that the mechanism behind ID in CHF is due to the depletion of iron stores and impaired iron metabolism as the inflammatory state of HF develops and progresses. Hepcidin has been further implicated in the pathogenesis of ID in CHF in response to the characteristic inflammation [30]. In association with HF, a TSAT $<20\%$ was associated with a lower peak oxygen consumption and an increased risk of mortality. ID has also been used to predict mortality independent of anemia [18].

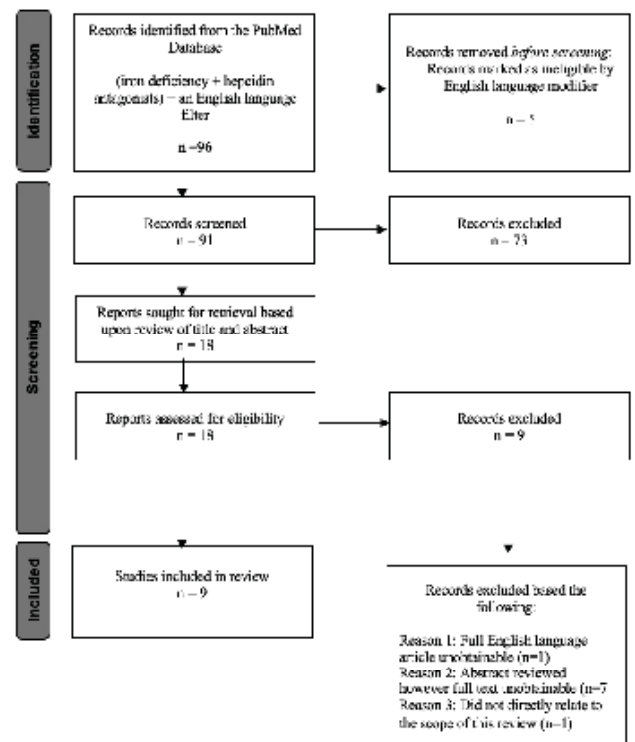


Figure 1: Methodology for selecting reviewed articles.



ID should be viewed as an independent comorbidity in HF and should be treated to improve the outcomes of patients with an HF diagnosis before reaching the anemia stage. ID is associated with decreased exercise tolerance, exertional hyperventilation, dyspnea, and worsened functional class [31]. It is closely related to disease progression and has been associated with increased NT-proBNP levels, the biomarker used to assess disease progression in HF. Moreover, ID has also been shown to increase the risk of death by 3-fold in those with HF independent of other outcome predictors, such as anemia [24,25,31]. It was demonstrated that those with Iron Deficiency Anemia (IDA) had a 2x increased risk of mortality than those who had iron-replete anemia [31]. ID has also been implicated in adverse cardiovascular events, inadequate bone marrow function, and remodeling in cardiomyocytes [23]. Furthermore, ID in HF has been connected to fibrosis, left ventricular hypertrophy (LVH), and diastolic dysfunction, as studied in animals [25,31]. ID has also been shown to drive catecholamine production, which has been a negative factor in the pathogenesis of CHF [31]. In conclusion, the above demonstrates the importance of treating ID prior to its progression to IDA.

As previously stated, iron studies are recommended in the initial laboratory workup when diagnosing and evaluating HF. As such, systematic implementation of ID evaluation and treatment is easily attainable prior to it reaching the anemia stage.

Anemia in HF

Anemia is a potential complication of ID and it poses an additional threat to the overall prognosis of HF. Anemia has been defined by the World Health Organization (WHO) as a Hb <13.0 g/dL in men and <12.0 g/dL in women [32]. In a study of 148 subjects, the majority of patients with both chronic heart failure and low hemoglobin (Hb) levels had anemia of chronic disease. This state was associated with defective iron supply in nearly all patients [33]. Ekezwitz, et al. [34] found that anemia was present in 17% of their hospitalized population with heart failure and of those 17%, 21% was due to defective iron supply [34]. Lastly, while anemia in patients with CHF is believed to be multifactorial, the most prevalent cause has been ID, though this may also be affected by hemodilution [23].

Factors involved in the pathogenesis of anemia in HF include iron utilization impairment, erythropoietin hyporesponsiveness, and depressed bone marrow function. It has been proposed that anemia's involvement in the progression of HF is due in part to increased cardiac workload. Anemia also exacerbates the other comorbidities common to HF [35]. Anemia in HF is more likely to affect the elderly and/or those with diabetes mellitus and CKD. It has also been connected with worsened HF state and prognosis, lower blood pressures, and increased neurohormonal and proinflammatory cytokine activity and activation [35]. Anemia was found to increase the relative risk of death in HF by 20% - 50% [32]. Okonko, et al. [31] determined that the etiology of anemia in HF patients is largely dependent upon the stage of HF and IDA was correlated with disease progression.

It is a developing hypothesis of the current review that treating ID prior to reaching the point of anemia is beneficial to overall disease progression. Studying this more closely is a potential avenue for further evaluation of the topic of ID without anemia in HF.

Treatment of ID and anemia in HF

Current methods for treating iron restriction anemias associated with hepcidin excess are oral iron supplementation, Erythropoietin Stimulating Agents (ESAs), and parenteral iron supplementation [17]. Goodnough, et al. [36] explored the different treatment possibilities for iron disturbances and other causes of anemia in various disease states. Table 3, which has been adapted from their manuscript, outlines this.

PO Supplementation options

Oral iron supplementation has been proposed as a possible treatment option for those with mild-moderate anemia or in those with iron-restricted erythropoiesis that has not been definitively ruled out. PO iron absorption has been inversely correlated with hepcidin levels, thus leaving hepcidin as a possible measurement for determining the candidacy of this treatment form [36]. Poor candidates could include those who have impaired iron absorption due to damage to the intestinal lining, celiac disease, and those on proton-pump inhibitor therapy [36]. Additionally, draw-backs with PO supplementation are rooted in absorption difficulties, poor tolerance, and compliance. Furthermore, erythropoietin supplementation has been advised against in patients with HFrEF as the risks are thromboembolic events and the benefit remains unclear [15]. Unfortunately, inflammatory states, like that seen in CHF, have been connected to erythropoietin resistance [19], raising concerns about the side effect profile of this treatment option.

Table 3: Available treatment options for iron dysregulation and various other causes of anemia [36].

Condition	Expected hepcidin profile	Current treatment recommendations	Hepcidin intervention feasibility
Absolute iron deficiency	Low	PO supplementation or IV supplementation if PO is not tolerated or malabsorption is suspected	No
Iron sequestration phenotype	High	IV combination with ESA therapy	Yes (Antagonist)
Mixed AI/IDA	Normal	IV	Yes (Antagonist)
Chronic kidney disease	High	IV in combination with ESA therapy or dialysis	Yes (Antagonist)
Functional iron deficiency	High	IV	Yes (Antagonist)
IRIDA	High	IV only	Yes (Antagonist)
Iron loading anemias	Low	Iron-chelation therapy	Yes (Agonist)
Iron loading anemias with transfusion	Normal to high	Iron-chelation therapy	Yes (Agonist)



ESAs

Historically, studies have reviewed and demonstrated an unfavorable side effect profile of ESAs. ESAs have been specifically studied in CKD and cancer patients [37] and have been linked with an increase in cardiovascular events and all-cause mortality [38]. Additional concerns were raised due to an increase in thromboembolic complications, hemorrhage, and hypertension in some patient populations [37]. Additional complications seen in HF include malnutrition and nutritional deficiencies, secondary hyperparathyroidism, hemolysis, and negative responses to commonly used medications for the treatment of HF, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEi and ARB, respectively) [38]. It has been stated that these side effects may be dose dependent [19] and hyporesponsiveness could alternatively explain the complications seen in HF [38]. Using an adjunct medication, such as a hepcidin antagonist/inhibitor, might help mitigate the dose dependency of these ESAs to make them safer and more effective for use in ID in HF [19].

Parenteral iron

A more promising technique has been IV iron supplementation formulations, which have been numerous and their efficacy has been extensively studied. IV iron supplementation has been recommended for the following classes: HFrEF with NYHA class III with an LVEF \leq 45%; HFrEF with NYHA class II with LVEF \leq 40% with a hemoglobin of 9.5 - 13.5, and ID as defined by serum ferritin $<$ 100 g/L OR transferrin saturation (TSAT) $<$ 20% OR serum ferritin 100-300 μ g/L AND TSAT $<$ 20% [15]. Iron supplementation has been largely recommended for symptom relief, to improve exercise tolerance, and to restore a subjectively acceptable quality of life [15].

Safety concerns of IV iron supplementation predominantly revolve around the risk of anaphylaxis and hypersensitivity reactions [37], both of which require close monitoring during infusions. In addition, cost and 6-H syndrome have been of concern. The 6-H syndrome has been summarized as high FGF23, hyperphosphaturia, hypophosphatemia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism. 6-H syndrome has been linked to osteomalacia, bone fractures, muscular weakness, and respiratory failure [37]. FGF23 increases urinary phosphate excretion and inhibits 1-alpha hydroxylase leading to vitamin D activation [37]. Lastly, there is concern as to the impact that the resulting electrolyte imbalances have on cardiomyocytes – another possible avenue for further research into treating ID and ID anemia in heart failure through IV treatments.

Yuan, et al. [39] have questioned the safety of IV iron supplementation as studied in end-stage renal failure patients on hemodialysis. They investigated and discovered that a small, yet not insignificant, amount of the iron supplied in parenteral administration was redox-active and was strongly associated with free radical production. Free radicals have been implicated in damage to cells and induction of cellular death. These effects would need to be further studied in HF patients, specifically.

These safety concerns for the current treatment options warrant investigation into other forms of treating ID. Hepcidin modulators are currently being studied and might offer a viable alternative.

Hepcidin antagonists/inhibitors

Hepcidin is involved in inflammation as an acute phase peptide, as demonstrated by the animal study completed by Nicolas, et al. [40]. It is activated and subsequently secreted in response to inflammation [9,17,19,26-28,30,32]. Hepcidin, which affects intestinal absorption of iron and diverts it into the reticuloendothelial system [30], most commonly responds to increased IL-6 via the JAK/STAT pathway [9,17,23,26,27]. Increased hepcidin leads to hypoferrremia in the body, resulting in decreased availability of iron for utilization in metabolic processes, ultimately leading to ID, and potentially, to ACD, or AI. Therefore, it is sensible to propose hepcidin antagonists and inhibitors as possible viable alternatives to proactively treating ID as a result of hepcidin overexpression in HF.

Fung, et al. [19] summarized completed animal model studies in an effort to provide evidence of feasibility for the use of hepcidin modulation as an alternative treatment for iron dysregulation conditions. Imposed overexpression of hepcidin in mice was studied in the treatment of hemochromatosis. Results indicated prevention of the typical iron overload. Similar effects were found while studying β -Thalassemia in a similar fashion. However unlike with hemochromatosis, modulating hepcidin in β -Thalassemia provided evidence for benefit in erythropoiesis – a prolonged red cell lifespan, improved hemoglobin levels, and a decrease in splenomegaly. In addressing induced anemia of inflammation, knocking out hepcidin in mice resulted in milder anemia symptoms and shorter recovery intervals. Lastly, in a similar fashion, knocking out the BMP receptor Alk3 (a regulator of hepcidin), anemia induction failed to decrease serum Hb concentration [19].

Currently, there are four proposed avenues to modulate hepcidin [26]. The mechanisms of action (MOA) of these modulators are summarized in Table 4, which contains information adapted from Nameth & Ganz [26].

Long-term effects and toxicities of hepcidin modulators

In a study completed by Sasu, et al. [41], hepcidin mRNA suppression or hepcidin neutralization techniques were able to overcome AI in mouse models, lending to the theory

Table 4: Mechanism of action of hepcidin antagonists by classification.

Hepcidin Antagonists	Class	MOA
Hepcidin antibodies	Class I	Hepcidin production inhibitors
Hepcidin neutralizing monoclonal antibodies	Class II	Hepcidin peptide inactivators/ sequestration
Hepcidin-Ferroportin interaction inhibiting monoclonal antibodies	Class III	Inhibitors of hepcidin binding to ferroportin
Currently under investigation	Class IV	Ferroportin modulators: prevention of ferroportin endocytosis or stimulating ferroportin production



that hepcidin modulators may be an option for modulating iron homeostasis. The same study suggested that hepcidin modulators redistribute iron throughout the body by releasing iron from storage for use in erythropoiesis and promoting intestinal absorption of iron [41]. A potential for hepcidin modulators is non-coagulant heparin. Due to heparin's long clinical use, its effects and safety are well known. Heparin without anticoagulation capabilities needs to further be studied in humans prior to implementation in clinical practice [21].

Conversely, some concerns regarding hepcidin modulators have been raised, though further studies in the realm of safety need to be completed. One safety concern is with humanized antibody antagonists that have previously been created. Though these compounds have been shown to have a long half-life, they are expensive to produce, raising concerns about the cost-benefit relationship. Additionally, other developed antagonists have questionable fates. siRNA agents involved in targeting hepcidin have been shown to have complex mechanisms of action and questionable specificity [21].

Based on this literature review, it is reasonable to consider hepcidin modulators as an alternative when treating iron deficiency in heart failure. However, further studies on safety profiles for hepcidin modulators need to be completed in human models. Some areas of further study have been raised in this literature review. These include human studies on the safety profile of hepcidin modulators, studying the effects of non-anticoagulant heparin in human trials, and studying the benefits of treating ID prior to reaching anemia more in-depth.

Conclusion

Iron deficiency caused by hepcidin excess due to the inflammatory state of heart failure is typically treated with IV and oral iron supplementation. However, historically, concerns regarding safety have been raised, including adverse CV events, anaphylaxis events, drug interactions, poor tolerance, and lack of compliance. Therefore, the current study has addressed ID in heart failure and suggested that hepcidin antagonists/inhibitors may provide a viable alternative to the classic iron deficiency treatment methods of oral iron and parenteral iron. Current studies are underway in studying the safety and efficacy of these modulators. Further human clinical trials need to be completed on the proposal that hepcidin antagonists/inhibitors are a reasonable alternative to IV and oral iron supplementation in the treatment of ID and ID anemia in HF patients.

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