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Treating Anemia of Chronic Disease

Sarit Fischer
Touro College

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Sarit Fischer Graduated with a Bachelor of Science degree in Biology in January 2020

Abstract

Anemia of chronic disease (ACD) is the result of altered iron metabolism, blunted erythropoiesis, and shortened red blood cell survival caused by inflammatory cytokines. Hepcidin plays a key role in anemia of chronic disease by inducing endocytosis of the iron exporter ferroportin. Iron is trapped in enterocytes, hepatocytes, and macrophages, and is unavailable for hemoglobin synthesis. When treating the underlying disease is not an option, or anemia is severe, ACD should be treated. While oral iron supplementation is not suitable for ACD, intravenous iron may be effective. Erythropoiesis stimulating agents are a common approach to treating ACD, but a large percentage of ACD patients are refractory to ESAs. Additionally, there are many safety issues associated with ESA therapy. Concomitant IV iron supplementation increases patient response to ESAs and may reduce safety concerns as well. Several new, more targeted approaches to ACD treatment are being studied. Isocitrate supplements have been shown to improve ACD by minimizing the iron restriction response to increase erythropoiesis. Antibodies such as infliximab and tocilizumab, which neutralize the inflammatory cytokines TNF-α and IL-6, respectively, decrease hepcidin expression and improve hemoglobin levels. Finally, antibodies and speigelmers that target hepcidin directly are being developed. These new therapies, alone or in combination with IV iron or ESAs, show promise in alleviating anemia of chronic disease.

Introduction

Iron is an essential element for life. From the smallest microbes to the most complex of organisms, all require this vital nutrient to survive. As such, one of our bodies' many host defense mechanisms is to limit the amount of iron available to pathogens. Inflammatory cytokines cause an increase in the expression of hepcidin, a liver protein that is a key regulator of iron metabolism. Hepcidin binds to ferroportin, the only known exporter of cellular iron, and causes it to be internalized and degraded (Nameth et al., 2004a). Thus, iron is trapped inside the cells, out of reach of bacteria, cancer cells, or other pathogens.

When inflammation becomes chronic, however, this innate defense mechanism becomes counterproductive. Too much of the iron from senescent red blood cells is sequestered within macrophages, rather than recycled for erythropoiesis. Patients with chronic inflammation often develop a unique form of anemia, known as the anemia of chronic disease (ACD). ACD is the second most common type of anemia, caused by some cancers, chronic infections such as HIV, autoinflammatory diseases such as rheumatoid arthritis, and other diseases that feature chronic inflammation such as inflammatory bowel disease or heart disease. While treatment for these patients must focus primarily on curing the underlying disease, treating the anemia may greatly improve the patients' quality of life. Because of the unique mechanism by which the anemia develops, treatment of ACD can be complicated. Treatments often used to treat other forms of anemia, such as iron deficiency anemia, may be ineffective, or even detrimental. This paper examines several possible approaches for treating anemia of chronic disease, given its unique pathogenesis.

Methods

The information in this article was compiled by review and analysis of articles located using PubMed, ProQuest, and Google Scholar. Access was provided by the Touro College Library system. Emphasis was placed on original studies, although review articles were also used. References cited in the articles provided further reading. Articles discussing anemia of chronic kidney disease (ACKD), a related but different disorder were not included in this review.

Discussion:

Pathogenesis of Anemia of Chronic Disease

Hepcidin is a small peptide containing multiple disulfide bonds that is secreted by the liver. It was first isolated from human urine (Park et al., 2001). Initially recognized for its anti-microbial properties, it soon became clear that hepcidin is a key regulator of iron metabolism. Iron-overloaded mice overexpress mRNA coding for a peptide closely homologous to human hepcidin. Additionally, iron depletion results in a decrease in hepcidin expression (Pigeon et al., 2001). Genetically modified mice overexpressing hepcidin were born with pale skin and died soon after birth. Those that survived had severe microcytic iron deficiency anemia (Nicolas et al., 2002a).

A 2004 study by Nameth et al. provided a breakthrough toward understanding the role of hepcidin in iron homeostasis. Using in vitro cells expressing ferroportin (Fpn) labeled with green fluorescent protein (Fpn-GFP), they demonstrated the effect of hepcidin on ferroportin. Hepcidin binds directly to Fpn, inducing its endocytosis. Upon addition of hepcidin, Fpn-GFP disappears from the cell surface, and is localized in intracellular vesicles. (Nameth et al., 2004a). Hepcidin binds directly to ferroportin and induces rapid ubiquitination of several lysine residues of ferroportin. This tags ferroportin for internalization (Qiao et al., 2012). Ferroportin is subsequently degraded by lysozymes.

Ferroportin (also called MTP-1) is an iron transporter located at the surface of cells involved in iron metabolism,

including duodenal enterocytes, hepatocytes, macrophages, and placental cells. It is structurally similar to the DMT1 class of metal transporters (Abboud and Haile, 2000). Ferroportin acts as an iron exporter, releasing iron into the bloodstream. Fpn null/null mice are not embryonically viable. Inactivation of ferroportin at birth results in severely anemic mice with accumulation of non-heme bound iron in enterocytes, macrophages, and hepatocytes (Donovan 2005). In vitro, cells expressing ferroportin only in the presence of an inducer, accumulate ferritin when ferroportin is inactive. Induction of ferroportin results in a clearance of ferritin from the cell (Nameth et al., 2004a).

There are no known cellular iron exporters other than ferroportin. The removal of ferroportin from the cell surface inhibits transport of iron to the serum. Iron is trapped within the cell and stored as ferritin. Hepcidin levels, and thus ferroportin levels, are modulated by serum iron levels. Iron overload activates a BMP (Bone Morphogenetic Protein)/ SMAD signaling pathway which causes increased hepcidin expression. Hemojuvelin, a protein that is mutated in juvenile hemochromatosis patients, plays an important role in this pathway as a coreceptor of BMP (Babbit et al., 2006). Hepcidin expression is downregulated in response to anemia and hypoxia, allowing the iron necessary for erythropoiesis to be released into the plasma (Nicolas et al., 2002b).

Hepcidin also increases as part of the acute phase response to inflammation. The inflammatory cytokine Interleukin-6 (IL6) is the primary inducer of inflammatory upregulation of hepcidin mRNA expression. In vitro, the increase of hepcidin stimulated by inflammation is inhibited by the addition of anti-IL6 antibodies. IL-6 infusion in humans causes an increase in urinary hepcidin, along with a decrease in serum iron and transferrin saturation (Nameth et al., 2004b). IL-6 activates a JAK/STAT signal transduction pathway. The immediate -165 base pairs of the hepcidin promoter are necessary for hepcidin induction by IL-6. Deletion of the STAT binding motif within this promoter fragment inhibits IL-6 activation. In particular, the transcription factor STAT3 is required (Falzacappa et al, 2007). Chronic inflammation results in increased hepcidin and anemia in WT mice, but not in STAT3 knockout mice (Sakamori et al., 2010).

In patients with chronically elevated IL-6, hepcidin is persistently elevated. The resulting lack of ferroportin causes iron to be retained within the cells. Dietary iron is not absorbed into the plasma. Iron stored in hepatocytes of the liver is not released. Most significantly, iron from senescent erythrocytes is sequestered in macrophages in the spleen. Rats with ACD had higher levels of ferritin in the spleen than healthy controls, with less iron being released from macrophages (Theurl et al., 2010). The resulting hypoferremia limits the amount of iron available for erythropoiesis.

In addition to the functional iron deficiency induced by hepcidin-mediated iron sequestering, inflammatory cytokines have been shown to have other effects which contribute to anemia of chronic disease. Specifically, Interferon-γ (IFN-γ) has been shown to suppress erythropoiesis. Inflammation inhibits the wave of reticulocytosis normally seen in cells treated with erythropoietin (Epo) in vitro. Neutralization of IFN-γ reverses this effect. Treatment of mice with anti-INF-γ antibodies prevents inflammatory suppression of erythropoiesis (Thawani et al., 2006). This blunting of erythropoiesis may explain why ACD is often normocytic and normochromic. Other anemias caused by inappropriately high hepcidin levels, such as iron refractory iron deficiency anemia, are severely microcytic and hypochromic. IFN-γ suppression of erythropoiesis seems to compensate for the lack of bioavailable iron by producing fewer normal RBCs, rather than many abnormal ones (Nameth & Ganz, 2014).

Further contributing to anemia, erythrocytes have a moderately shortened life span in inflammatory conditions. Biotin labeling of erythrocytes in mice showed a complete RBC turnover by day 15 in mice with inflammation, compared to day 36 in control mice (Thawani et al., 2006). In humans, erythrocyte life span in patients with rheumatoid arthritis (RA), often used as a model for ACD, is significantly shorter than in healthy controls. Red blood cells from these patients transfused into healthy individuals showed normal survival. This indicates that the shortened survival was not caused by defects in the red blood cells. Rather, inflammation causes a decrease in erythrocyte life span by some extrinsic mechanism (Freireich et al., 1957). The premature destruction of erythrocytes is likely the result of increased macrophage activity in the spleen in response to various cytokines (Nameth & Ganz, 2014).

Tumor Necrosis Factor (TNF-α) and Interleukin-1 (IL-1) were among the earliest inflammatory cytokines to be implicated in anemia of chronic disease. However, the mechanisms involved are still unclear. Both TNF-α and IL-1 reduce hepcidin expression in vitro (Song et al., 2013). It seems that their role in ACD is indirect, via regulation of other cytokines. Cytokine-cytokine interactions are complex, and researchers still have a lot to learn before the pathogenesis of ACD can be fully understood.

Treating Anemia of Chronic Disease

Anemia of chronic disease is a secondary effect of an underlying illness. ACD is usually mild. As such, the major focus of treatment protocols for ACD patients must be on

curing the primary disease. As the inflammation caused by the disease subsides, inflammatory cytokine levels return to baseline. Consequentially, the anemia will be resolved without the need for anemia-related treatment. However, often the underlying disease is not curable. Anemia may also have a profound negative impact on the patient's quality of life. The most common complaint of patients with ACD is fatigue, which can be debilitating. In such cases, direct treatment of the anemia of chronic disease is recommended. As with any medical intervention, the benefits of treatment must be weighed carefully against any possible risks. It is important to note that anemia in chronically ill patients is often multifactorial. Anemia of chronic disease may occur in conjunction with true iron deficiency anemia, or anemia of another cause. It is necessary to correctly diagnose the cause of anemia before deciding on a treatment option. Finally, certain treatments may not be suitable for certain patients, depending on which underlying disease is causing the inflammation.

Oral iron supplementation, the obvious solution for iron deficiency anemia, is not appropriate for anemia of chronic disease. The removal of ferroportin from the basolateral surface of duodenal enterocytes prevents oral iron from being adequately absorbed into the plasma. Much of the minimal iron that is absorbed will be diverted into hepatocytes (Weiss & Goodnough, 2005). Intravenous iron therapy may be effective in treating anemia of chronic disease, because parenteral administration allows it to bypass the "mucosal block" in the duodenum. Indeed, several trials have shown that IV iron therapy is beneficial for anemia of chronic disease in cancer patients. A pilot study showed a significant increase in hemoglobin levels in cancer patients with non-iron deficiency anemia in response to weekly doses of ferric hydroxide sucrose (Abdel-Rezeq et al, 2013). A single dose of ferric carboxymaltose improved hemoglobin levels in chemotherapy patients with ACD. This improvement was maintained for a minimum of 8 weeks. (Hedenus et al., 2014). A large study comparing the efficacy of IV iron and oral iron supplementation in cancer patients found that both treatment options induce a similar increase in hemoglobin levels, although the response time was faster for IV iron. IV iron also caused less side effects than oral iron. The efficacy of oral iron seen in this study is surprising, as it conflicts with many other studies. However, this study included patients with iron deficiency anemia (Birgegard et al, 2016). Trials that were specific to patients with functional iron deficiency showed IV iron to be superior.

Several concerns have been raised regarding the safety of iron supplementation. Iron overload is associated with oxidative stress and cardiovascular events. Additionally, iron sequestering is an innate host defense mechanism. Iron supplementation may increase the risk of infections and tumor growth. (Weiss & Goodnough, 2005). Although the trials reported here have indicated that intravenous iron is safe for cancer patients, these trials only followed patients for short periods of time. Long-term studies are necessary to establish whether IV iron is truly safe for patients with anemia of chronic disease (Rodgers & Gilreath, 2019). Most of the research regarding efficacy of IV iron monotherapy for anemia of chronic disease has been in chemotherapy patients. Further experimentation is necessary to assess whether parenteral iron is useful in cases of ACD caused by illnesses other than cancer.

Among the earliest treatment options available for anemia of chronic disease are Erythropoiesis Stimulating Agents (ESAs). This category includes recombinant human erythropoietin (rHuEpo) and its derivatives, Epoetin-α and Darbepoetin-α. ESAs target the blunted erythropoiesis characteristic of ACD and should minimize the iron-sequestering effect of hepcidin as well. Pharmacological levels of erythropoietin cause a dose-dependent decrease in hepcidin expression in vitro (Pinto et al., 2008). In another study, pretreatment with erythropoietin partially prevented the increase in hepcidin normally induced by inflammation in mice. This effect was dose dependent. Pharmacological doses of Epo were effective, but the endogenous increase in erythropoietin in response to hypoxia was insufficient to reduce hepcidin expression. IL-6 levels were similar in Epo-treated and control mice. However, STAT3 phosphorylation decreased significantly. Suppression of STAT3 is likely the mechanism by which erythropoietin decreases IL-6 induced hepcidin expression (Huang et al., 2009). Erythropoiesis stimulating agents have been proven effective for ameliorating anemia of chronic disease in humans. In a placebo controlled double blind trial, normal hemoglobin levels were achieved in 94% of rheumatoid arthritis patients with ACD treated with rHuEpo. Interestingly, rHuEpo also reduced disease activity in RA patients (Peeters et al., 1996). ESAs are likewise used to treat anemia of chronic disease in cancer patients.

Unfortunately, there are serious safety concerns regarding ESAs. Although few side effects were reported in early trials of ESAs for rheumatoid arthritis patients (Peeters et al., 1996, Nordström et al., 1997), ESA treatment is associated with numerous adverse effects, especially in cancer patients. In a meta-analysis of 53 trials including close to 4,000 patients, mortality increased by 17% in cancer patients with anemia treated with ESAs compared to controls (Bohlius et al., 2009). In 2007, the FDA issued a black box warning stating that "ESAs

increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence [in cancer patients]". Venous thromboembolism is one of the most prevalent adverse effects of ESAs. This may be because ESAs induce iron-deficient erythropoiesis (IDE), by increasing erythropoiesis despite the lack of bio-available iron caused by ACD. This results in elevated platelet counts, which increases the risk for thrombolytic events (Henry et al., 2011).

Aside from increased safety concerns, the functional iron deficiency of ACD limits the efficacy of ESAs. Many patients do not respond to ESA treatment. Response rates vary from trial to trial. One study, in RA patients, reported that only 14.6% of patients achieved target hemoglobin levels. Decreased iron levels and more severe inflammation were predictive of a poor response. In an extension to the study, four out of five initial non-responders who were now given iron supplementation in addition rHuEpo treatment did show significant improvement in hemoglobin levels (Nordström et al., 1997). Hemoglobin does not increase significantly in response to ESAs in mice overexpressing hepcidin (Sasu et al., 2010). In another study, rats with higher pre-treatment levels of hepcidin, which correlates to lower iron availability, were shown to respond poorly to ESA treatment. Although ESAs decrease hepcidin expression somewhat, and thus decrease splenic iron retention, this effect is inadequate. Serum iron remains low, and ESA treatment does not effect an increase in hemoglobin in rats with very high hepcidin levels (Theurl et al., 2014).

The limitations of iron-deficient erythropoiesis to ESA treatment has led researchers to investigate whether concomitant iron supplementation could improve the safety and efficacy of ESAs. Indeed, many studies have shown positive results when erythropoiesis stimulating agents are combined with intravenous iron. Parenteral iron administration is preferable to oral supplements, as oral iron is not well absorbed by patients with ACD. IV iron could correct ESA-induced iron-deficient erythropoiesis and improve response to rHuEpo in rheumatoid arthritis patients with anemia of chronic disease (Arndt et al., 2005). Encouraging results were seen in cancer patients with ACD as well. Patients receiving supplemental iron intravenously achieved higher hemoglobin levels in response to epoetin-α than patients receiving epoetin-α with oral iron or epoetin-α alone. Response rates were significantly improved in the IV iron group as well. In the IV iron group, 73% of patients responded to the ESA treatment, compared to only 45% and 41% in the oral and no iron groups, respectively (Henry et al., 2007). Auerbach et al. similarly reported that cancer patients who received combination of darbepoetin-α and IV iron were more likely to reach target hemoglobin levels, with more rapid and significant improvement than patients who did not receive IV iron. Interestingly, the incidence of adverse effects, including thrombolytic events, was similar in both groups (Auerbach et al., 2010). By contrast, post-hoc analysis of data from the first study showed that IV iron decreased the likelihood of elevated platelet counts and venous thromboembolism (Henry et al., 2011). One trial failed to show a significant difference between chemotherapy patients receiving darbepoetin and intravenous ferric gluconate versus oral iron or oral iron placebos. Additionally, many adverse events were reported among those patients receiving parenteral iron (Steensma et al., 2010). However, this study had several limitations. The overall iron dose was lower than in other studies, potentially limiting the benefit of IV iron. By contrast, the individual doses of iron administered were 50% above the recommended dosage, which may explain the excessive number of adverse events. Finally, the study was terminated early, with few patients completing the study (Steensma et al., 2010 & Aapro et al., 2011). Nevertheless, the high incidence of adverse events in this study highlights the need for additional studies as to the safety of parenteral iron.

Experimental Treatment Options

Another option for targeting the blunted erythropoiesis of ACD which is currently being studied is isocitrate supplements. Aconitase is a Krebs's cycle enzyme responsible for converting citrate into isocitrate. Insufficient iron levels result in decreased aconitase activity, to produce less isocitrate. Aconitase activity is used by the body as an "iron sensor". Decreased isocitrate results in downstream inhibition of erythropoiesis by sensitizing erythroid progenitor cells to the inhibitory effects of IFN-γ (Richardson, et al., 2013). This is known as the iron restriction response. Supplementation of exogenous isocitrate inhibits the iron restriction response via a PKC mechanism (Bullock et al., 2010). Isocitrate does not change serum or stored iron levels, nor does it alter erythropoietin levels (Kim et al., 2016). Rather, it seems to "fool the system" into increasing erythropoiesis despite hypoferremia.

Low doses of isocitrate supplementation reversed anemia of inflammation in a model of rat arthritis by preventing the iron restriction response (Richardson et al., 2013). However, later studies found that much higher doses were necessary to achieve even transient results in mice. Administration of high doses of isocitrate caused increased inflammation in these mice (Kim et al., 2016).

The necessity of such high doses to improve anemia of chronic disease may limit the efficacy of isocitrate as a treatment for ACD in humans. Recent research has shown that treatment with a combination of isocitrate and fumarate is effective in curing anemia of chronic disease in a murine model, even at low doses (Goldfarb et al., 2019). Further research, including human trials, is necessary to determine whether isocitrate may be a clinically appropriate treatment for ACD. It seems reasonable to assume, however, that isocitrate treatment may have limitations similar to those seen with ESAs, as bypassing the iron restriction response would lead to iron deficient erythropoiesis. As with ESAs, supplementation with IV iron may be beneficial.

ACD is caused by the result of the interaction of various cytokines. Recent research has focused on inhibition of these inflammatory signals using humanized antibodies as a target for treating anemia of chronic disease. Inhibition of Tumor Necrosis Factor-α (TNF-α) is a common treatment option for the auto-inflammatory disease Rheumatoid Arthritis. Treatment with infliximab, an anti-TNF-α antibody, reduces hepcidin levels and improves blood parameters in RA patients. TNF-α alone actually decreases hepcidin mRNA expression in vitro. Paradoxically, TNF-α also upregulates IL-6 production, resulting in the downstream upregulation of hepcidin. Inhibition of TNF-α reduces IL-6, thereby indirectly reducing serum hepcidin levels, albeit not as effectively as direct inhibition of IL-6 (Song et al., 2013).

Tocilizumab, an IL-6 inhibitor used to treat multicentric Castleman's disease (MCD) and rheumatoid arthritis, effectively reduces anemia of chronic disease in these patients. Tocilizumab is a humanized anti-IL6 receptor antibody. It binds to the IL-6 receptor and prevents IL-6 binding (Mihara et al., 2011). Tocilizumab completely inhibits IL-6 induction of hepcidin expression in vitro. Short-term treatment of MCD patients with tocilizumab results in decreased hepcidin and amelioration of anemia. These results continue when Tocilizumab was given over a longer period of time. Hepcidin expression keeps decreasing until normal serum hepcidin levels are reached and hemoglobin increases. Other iron-related parameters improve as well (Song et al., 2010). Tocilizumab decreases serum hepcidin and improves iron related blood parameters including hemoglobin, serum iron, ferritin, and MCV in rheumatoid arthritis patients as well (Song et al., 2013). In monkeys with anemia of chronic disease, IL-6 blockade with tocilizumab caused a rapid decrease of serum hepcidin. Hemoglobin levels and RBC improvement was drastic at first, then slowed and gradually continued until they returned to pre-inflammation levels (Hashizume 2010). The amelioration of anemia by tocilizumab seems to be due to inhibition of IL-6 induction of hepcidin. However, as IL-6 plays a role in the pathogenesis of MCD and RA, and tocilizumab reduces disease symptoms, it may be that the improvement of the underlying disease plays a role in decreasing anemia as well.

A major concern with tocilizumab treatment is its immunosuppressive effect and increased risk of infection. Additionally, since tocilizumab suppresses biomarkers of infection, it is necessary to observe patients closely for symptoms that may indicate infection (Mihara et al., 2011). The STREAM study, which followed RA patients receiving tocilizumab monotherapy over a period of five years showed the drug to have a good safety profile. The majority of the adverse events reported were mild, and the benefits of the drug on patient quality of life outweighed these events (Nishimoto et al., 2009). It remains to be seen whether tocilizumab and other anti-cytokine antibodies are safe and effective for treating ACD caused by other diseases.

Perhaps the most targeted approach to treating ACD is direct inhibition of hepcidin activity. Monoclonal antibodies (mAbs) and speigelmers which bind to hepcidin and prevent its interaction with ferroportin are promising developments. A Phase-1 study of the anti-hepcidin mAb LY2787106 in humans showed that the antibody was safe and well-tolerated in cancer patients with few serious adverse effects reported. However, the drug elicited only a transient increase in serum iron, which did not translate into improved hepcidin, serum ferritin, and TSAT levels (Vadhan-Raj et al., 2017). While ineffective alone, this antibody may be useful in treating ACD in combination with other drugs.

As an alternative to antibodies, Noxxon Pharma of Germany has developed an anti-hepcidin speigelmer called Lexaptepid Pegol (Nox-H94). Speigelmers are oligoribonucleotides with L-stereochemistry which bind to the target protein and inactivate it in a manner similar to antibodies. The advantage of a speigelmer over antibodies is that it does not elicit an immunological response in patients. Its L-stereochemistry prevents the development of anti-drug antibodies (ADAs) and also makes it nuclease resistant (Schwoebel et al., 2013). Indeed, patients receiving lexaptepid did not form antibodies specific to the drug (Boyce et al., 2016), while some patients receiving the mAb LY2787106 did develop ADAs (Vadhan-Raj et al., 2017). In vitro, lexaptepid inhibits the hepcidin-induced decrease in ferroportin expression. In monkeys with ACD caused by IL-6 injection, lexaptepid pegol partially improved reticulocyte hemoglobin levels, hematocrit, and erythrocyte counts (Schwoebel et al., 2013). A

placebo controlled double blind study of lexaptepid pegol in healthy humans showed a dose-dependent increase in serum iron, transferrin saturation, and serum ferritin. Reticulocyte hemoglobin did not increase in healthy volunteers but would be expected to increase in patients with ACD (Boyce et al., 2016). Lexaptepid temporarily prevents the inflammation-induced hypoferremia caused by endotoxin injection in heathy individuals (van Eijk et al., 2014). While the results have been promising in trials involving healthy individuals, further trials in ACD patients are necessary in order to know whether Lexaptepid can be clinically useful.

One aspect which may limit the effectiveness of both anti-hepcidin antibodies and speigelmers is the relatively high production rate of hepcidin. High doses of these hepcidin-binding ligands are necessary to keep up with production of new hepcidin (Fung & Nameth, 2013). Further experimentation, particularly in patients with anemia of chronic disease, will show whether this indeed limits the clinical value of such treatments. Even if these drugs are ineffective alone, they may be useful in combination with other treatments. Low dose antibody neutralization of hepcidin was shown to increase responsiveness to ESAs in mice with ACD. The combination of the antibody and darbepoetin-α completely corrected anemia in these mice (Sasu et al., 2010). If this is shown to be the case in humans as well, these drugs could take the place of parenteral iron, thereby eliminating the potential safety hazards associated with IV iron.

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