REVIEW ARTICLE

Anemia of Inflammation

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

From the Departments of Medicine and Pathology, David Geffen School of Medicine at UCLA, Los Angeles. Address reprint requests to Dr. Ganz at the David Geffen School of Medicine at UCLA, 43-229 CHS, Box 951690, 10833 LeConte Ave., Los Angeles, CA 90095, or at tganz@mednet.ucla.edu.

ANEMIA OF INFLAMMATION (ALSO REFERRED TO AS ANEMIA OF CHRONIC disease) has been recognized for more than 60 years as a mild to moderately severe anemia (hemoglobin level, 7 to 12 g per deciliter) that develops in the context of systemic inflammation because of decreased production of erythrocytes, accompanied by a modest reduction in erythrocyte survival.[1] The disorder, like iron-deficiency anemia, is characterized by low serum iron levels (hypoferremia), but it differs from iron-deficiency anemia in that iron stores are preserved in marrow macrophages, as well as in splenic and hepatic macrophages that recycle senescent erythrocytes. Thus, anemia of inflammation is primarily a disorder of iron distribution.[1]

Whereas erythrocytes in iron-deficiency anemia are often small (low mean corpuscular volume) and hemoglobin-deficient (low mean corpuscular hemoglobin concentration), the erythrocytes in anemia of inflammation most often appear normal, although they become small and pale in a subset of patients, particularly those in whom iron deficiency coexists or develops as a complication. The normal lifespan of human erythrocytes is about 120 days, and even if the lifespan is somewhat decreased by inflammation, a clinically significant decrement in the erythrocyte count does not usually develop until weeks to months after the onset of the underlying inflammatory disorder, accounting for the association of anemia of inflammation with chronic diseases. In critically ill patients, however, anemia of inflammation can develop very rapidly, after 1 week in a critical care unit.[2] In such patients, the progression of anemia of inflammation is often accelerated by concomitant blood loss (iatrogenic or disease-associated) or hemolysis, processes that rapidly unmask the suppressive effect of inflammation on the erythropoietic system and its inability to augment erythropoiesis in response to the loss of erythrocytes.[3,4]

Anemia of inflammation and iron-deficiency anemia are the two most common anemias worldwide, and they are often coexisting disorders in people who live in developing countries with a high prevalence of nutritional deficiencies and infections.[5] In populations with better access to medical care and iron-rich nutrients, anemia of inflammation is classically associated with chronic systemic inflammatory disorders, including rheumatoid arthritis and systemic lupus erythematosus; inflammatory bowel disease; chronic infections, including tuberculosis and the acquired immunodeficiency syndrome; hematologic cancers associated with increased cytokine production, such as Hodgkin's lymphoma and some types of non-Hodgkin's lymphoma; and certain solid tumors (e.g., ovarian cancer and lung cancer). Increasingly, anemia of inflammation is recognized as the main or contributing cause of anemia in many other patients with systemic inflammation, including those with chronic kidney disease,[6] chronic heart failure,[7] chronic obstructive pulmonary disease,[8] or cystic fibrosis.[9]

INFLAMMATION

Inflammation is a set of biologic mechanisms that evolved in multicellular organisms to constrain and neutralize infectious and other injurious agents that entered the tissues. The initial recognition of such agents is mediated by molecular sensors on membranes of host defense cells, in cellular cytoplasm, or in extracellular fluid (e.g., toll-like receptors, Nod-like receptors, and mannose-binding lectin). On contact with specific molecular patterns that are characteristic of infectious or injurious agents, the activation of these molecular sensors generates mediators that eventually give rise to the clinically detectable manifestations of inflammation. In addition, inflammation may develop as a result of immune dysregulation in autoimmune or malignant disorders (e.g., rheumatologic disorders, inflammatory bowel disease, and Hodgkin's lymphoma). Whether the aging process itself causes dysregulation of inflammation, even in the absence of a specific inflammatory disease, remains controversial.[10] Cytokines, including tumor necrosis factor α (TNF-α), interleukin-1, interleukin-6, and interferon-γ, are produced by inflammatory cells within the first hours after the onset of inflammation; these cytokines restrict erythropoiesis both directly and indirectly and shorten the erythrocyte lifespan.
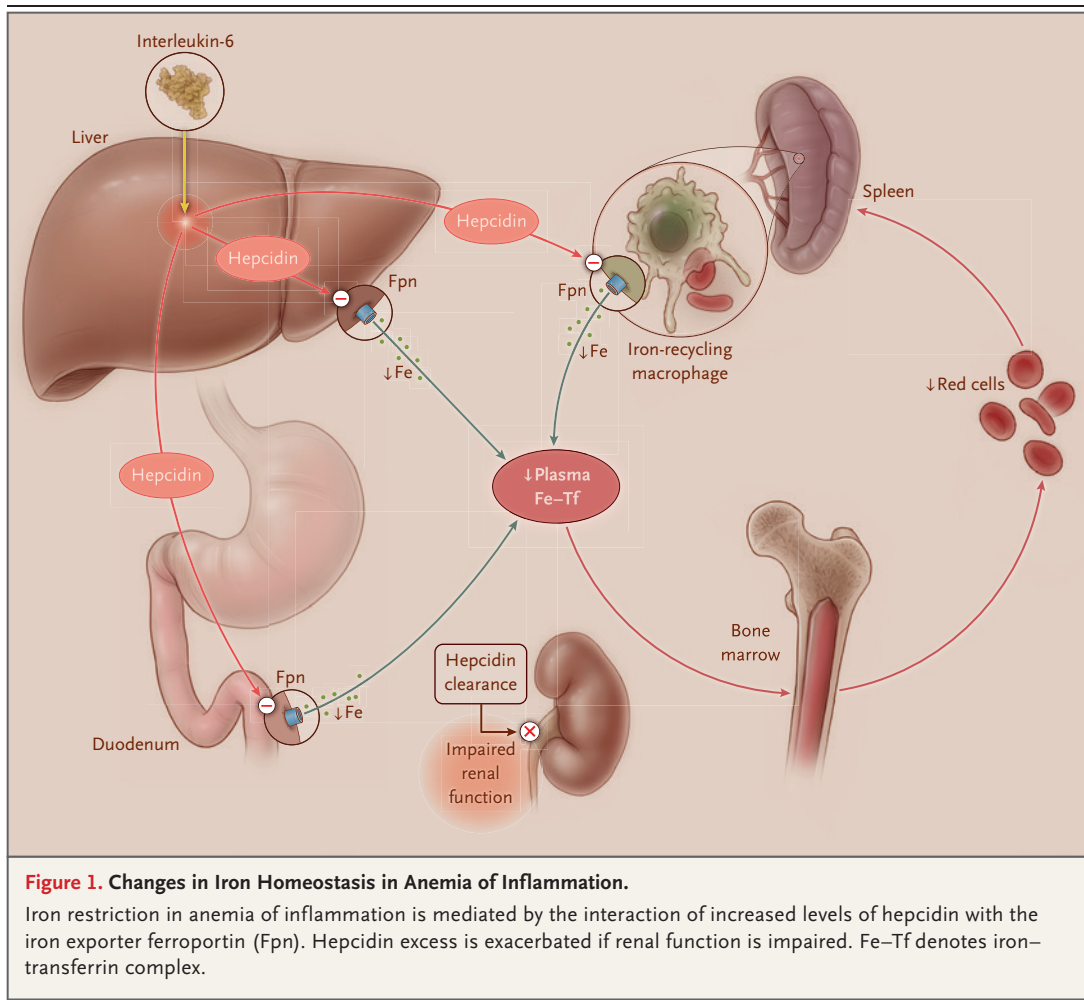
IRON METABOLISM

During normal erythropoiesis, when there is an adequate nutritional iron supply and an absence of inflammation, systemic iron homeostasis maintains plasma iron levels in the range of 10 to 30 μM and whole-body iron stores in the range of 0.3 to 1 g, with the lower end of the ranges typical for women of reproductive age. The main mechanism of iron homeostasis centers on the interaction between the iron regulatory hormone hepcidin, produced by hepatocytes, and ferroportin, which is both the hepcidin receptor and the sole cellular iron exporter through which iron is transferred to blood plasma[11] (Fig. 1). Hepcidin inhibits the iron-exporting activity of ferroportin, thereby controlling the transfer of iron to blood plasma from iron-absorbing duodenal enterocytes, from macrophages that recycle the iron of senescent erythrocytes, and from iron-

storing hepatocytes. Plasma iron is bound to the transport protein transferrin and is mostly destined for delivery to marrow erythroblasts that consume iron to synthesize heme and hemoglobin, with smaller iron flows meeting the iron requirements of all other organs and tissues. Baseline hepcidin synthesis is controlled by feedback from both iron stores and plasma iron levels.

The hepatic iron regulatory system is based on complex and incompletely understood interactions between at least two types of iron sensors in the liver that interact with the hepatocyte bone morphogenetic protein receptor and affect the signaling pathway that transcriptionally regulates hepcidin synthesis.[12] The two types of iron sensors detect the level of diferric transferrin in plasma (transferrin receptors 1 and 2) and the amount of iron stored in the liver (sensor not yet identified), respectively. These iron-sensing mechanisms increase hepcidin synthesis when iron levels are abundant and decrease it during iron deficiency, thereby modulating dietary iron absorption and release from stores in response to iron status. Inflammation greatly increases hepcidin synthesis, which is important in the pathogenesis of anemia of inflammation. Hepcidin synthesis increases predominantly but not exclusively[13] because of interleukin-6,[14] which acts through the JAK2–STAT3 (Janus kinase 2–signal transducer and activator of transcription 3) pathway to increase the transcription of the hepcidin gene in hepatocytes. Although small but clinically relevant increases in serum hepcidin develop even in relatively mild systemic inflammatory states, such as obesity,[15] serum hepcidin levels may increase by a factor of more than 10 in patients with sepsis as compared with healthy persons.[16]

ERYTHROPOIESIS

Erythrocytes are generated from hematopoietic stem cells in the marrow through steps involving progressively more restricted lineage choices[17] and decreasing proliferative capacity.[18] Although the specific pathways controlling these lineage choices are still not fully understood,[19] it appears that some populations of early progenitors have the potential for both myeloid differentiation and erythroid or megakaryocytic differentiation, with the path choice biased by mutually antagonistic
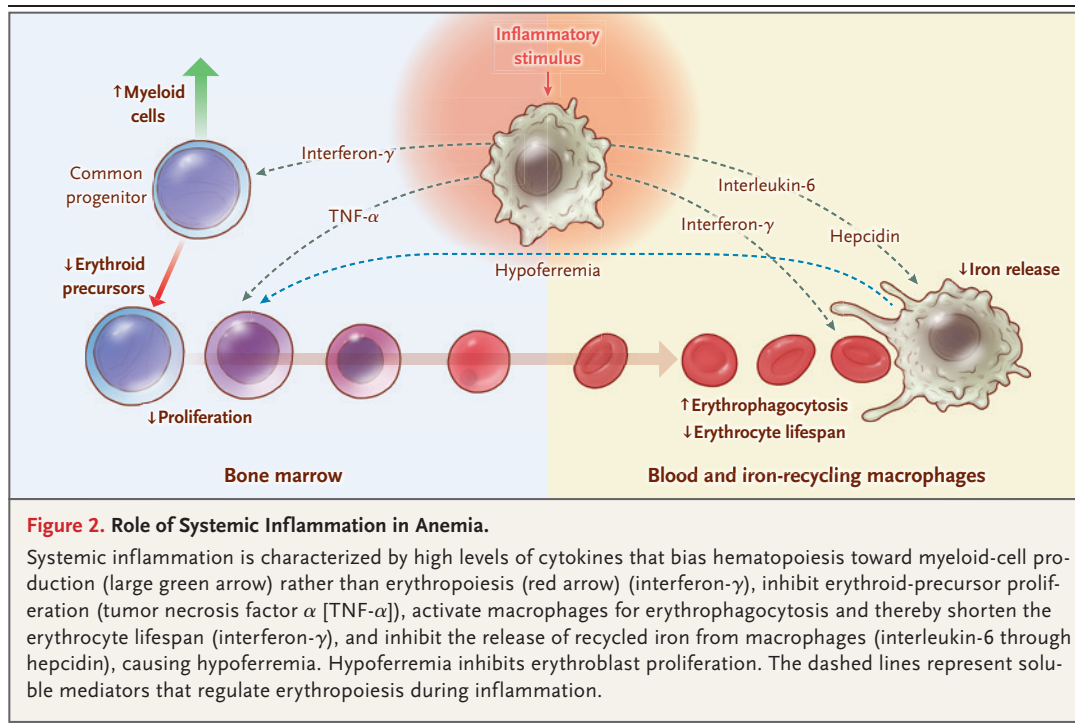
Figure 1. Changes in Iron Homeostasis in Anemia of Inflammation.

Iron restriction in anemia of inflammation is mediated by the interaction of increased levels of hepcidin with the iron exporter ferroportin (Fpn). Hepcidin excess is exacerbated if renal function is impaired. Fe–Tf denotes iron–transferrin complex.

interactions between two transcription factors: PU.1, which favors myeloid differentiation, and GATA1, which favors erythroid differentiation.[17] The relative proportions of the two transcription factors can be influenced by inflammation. The first precursor fully committed to erythroid differentiation is BFU-E (burst-forming unit, erythroid), defined by the ability of these cells to proliferate and give rise to large clusters of erythroid cells when cultured in semisolid medium with appropriate growth factors. A more differentiated cell type is CFU-E (colony-forming unit, erythroid), which generates fewer erythroid cells under these conditions.[18] CFU-Es give rise to even more differentiated proerythroblasts. Each proerythroblast then undergoes four or five more divisions, each of which yields progressively more mature hemoglobin-synthesizing erythroblasts, finally enucleating to yield reticu-

locytes, which are marked by their residual RNA content. In blood, reticulocytes mature into biconcave erythrocytes. The survival rate of CFU-Es and early erythroblasts is determined by erythropoietin, and the differentiation and division of erythroblasts are controlled by the levels of erythropoietin and iron,[20] as well as by one or more activin-like members of the TGF-β (transforming growth factor β) superfamily.[21] Erythropoiesis is dependent on the level of diferric transferrin in plasma, a factor that is relevant to the pathogenesis of iron-restrictive anemias.

PATHOGENESIS

EVOLUTIONARY PERSPECTIVE

Responding to infection or injury by favoring host defense processes over housekeeping processes such as erythropoiesis is a beneficial

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.

evolutionary strategy that provides a useful framework for understanding anemia of inflammation. Hypoferremia and increased production and activation of leukocytes serve host defense at the expense of erythrocyte production and erythrocyte survival. Increased production of leukocytes and hypoferremia diminish the number of erythroid precursors, and macrophage activation shortens the erythrocyte lifespan (Fig. 2). The long lifespan of erythrocytes buffers the consequences of decreased erythropoiesis during most acute infections. In chronic infections or inflammatory disorders, erythrocyte counts are often reduced to an anemic steady state in which the destruction of erythrocytes matches their decreased production, a condition that has been very difficult to model in laboratory rodents.

HYPOFERREMIA

Hypoferremia develops within the first few hours after infection or other inflammatory events. The decreases in the plasma iron level and transferrin saturation may serve to prevent the generation of nontransferrin-bound iron, an iron species now recognized as a potent stimulus to the pathogenicity of gram-negative bacteria[22,23] and probably other microbes as well. Plasma and other extracellular fluid, which are the compartments invaded during infections with extracellular bacteria, contain only 2 to 3 mg of iron, as compared with 3 to 4 g of total body iron, and their iron content turns over every few hours, making the plasma iron level potentially unstable when the iron supply or demand changes. Erythropoiesis represents the main consumer of iron from plasma, and the recycling of senescent or damaged erythrocytes by macrophages is the main source of iron for plasma. Both are strongly affected by various inflammatory processes, making tight control of the iron level during inflammation particularly important for host defense. High levels of circulating hepcidin, stimulated by interleukin-6, inhibit the export of cellular iron into plasma, thereby decreasing both intestinal absorption of iron and the release of iron from erythrocyte-recycling macrophages in the spleen and the liver. Macrophages and hepatocytes, the two cell types that accumulate iron, secrete large amounts of ferritin through nonclassical secretory mechanisms.[24] Hypoferremia associated with elevated plasma ferritin and hepcidin levels is characteristic of anemia of inflammation, whereas in iron-deficiency anemia, hypoferremia associated with low plasma ferritin and hepcidin levels is characteristic.

Inflammatory hypoferremia, like the hypofer-

remia of systemic iron deficiency, has an inhibitory effect on erythropoiesis. Iron is not simply stoichiometrically limiting for hemoglobin synthesis, in which each hemoglobin molecule requires four iron atoms. Rather, erythropoiesis is inhibited by hypoferremia[25,26] at a relatively high set point (transferrin saturation of 15 to 20%) in a manner that appears to protect the iron supply for other tissues (e.g., muscle, central nervous system, and nonerythroid marrow), which are less affected by the decreased plasma iron level.

BONE MARROW REPROGRAMMING

Leukocytosis and increased production of leukocytes in the marrow are early inflammatory responses, manifested in the marrow by an increased number of myeloid precursors (ratio of myeloid to erythroid precursors, >4:1). Such reprogramming of the marrow is mediated by inflammatory cytokines (e.g., TNF-α[27] and interferon-γ,[28] which have been studied most extensively) that activate the transcription factor PU.1 to promote myelopoiesis and lymphopoiesis at the expense of erythropoiesis. The capacity of BFU-E to give rise to more differentiated erythroid cells is also inhibited by inflammatory cytokines.[29,30]

Another form of marrow reprogramming is mediated by inflammatory suppression of erythropoietin, the master erythropoietic hormone. Serum erythropoietin levels are reduced in a subgroup of patients with systemic inflammation,[31,32] at least as compared with patients who have a similar degree of iron-deficiency anemia. The plausibility of a mechanism that is dependent on the effect of inflammation on erythropoietin-producing renal interstitial cells is supported by experiments in murine models.[33] The responsiveness of erythroid precursors to erythropoietin is also impaired by inflammation, as commonly manifested by increased exogenous erythropoietin requirements in patients with end-stage kidney disease who have inflammation.[34,35] The resistance to erythropoietin is mediated in part through a decrease in the number of erythropoietin receptors on erythroid progenitors, which is a recently described effect of hypoferremia that results in a diminished proliferative capacity of these progenitors.[20]

SHORTENED ERYTHROCYTE LIFESPAN

In patients with anemia of inflammation, a moderate (approximately 25%) decrease in the erythrocyte lifespan, to approximately 90 days, has been consistently shown, originally with the use of radioactive iron tracers[36] and currently by means of measurements of exhaled carbon monoxide,[37] a product of heme degradation. A decreased erythrocyte lifespan is also seen in many patients with inflammation who do not have anemia,[37] so anemia will develop only when the erythropoietic compensation is impaired. The heterogeneity of underlying diseases in anemia of inflammation makes it likely that multiple factors contribute to the increased destruction of erythrocytes, including macrophage activation[28] (which may affect the threshold for recognition of erythrocyte senescence) and exposure of erythrocytes to bystander inflammatory damage.[38] The term "consumptive anemia of inflammation" refers to disorders in which hemophagocytosis by activated macrophages is the predominant cause of anemia.[39] Extrapolating from frank hemolytic anemias associated with infections and severe systemic inflammation, erythrocytes are likely to be damaged even in anemia of inflammation by the deposition of antibody and complement and injury from microvascular fibrin strands.

DIAGNOSIS OF ANEMIA OF INFLAMMATION

Symptoms of mild-to-moderate anemia in patients with anemia of inflammation include fatigue, exercise intolerance, and exertional dyspnea, but these symptoms are difficult to distinguish from the effects of chronic systemic inflammation. Anemia of inflammation is diagnosed in patients with normocytic and normochromic anemia (normal mean corpuscular volume and normal mean corpuscular hemoglobin concentration, respectively) in whom there is evidence of systemic inflammation (increased erythrocyte sedimentation rate or C-reactive protein level) and evidence of iron restriction that is not caused by systemic iron deficiency (low transferrin saturation [<20%] along with a high serum ferritin level [>100 μg per liter]). The main challenge in establishing a specific diagnosis is the common coexistence of true iron deficiency and anemia of inflammation (especially in patients with blood loss from underlying disease) or an iron deficit caused by malnutrition, long-standing inflammation, or increased iron requirements (in growing children or pregnant women).

Differences in biomarkers of anemia of inflammation and true iron deficiency are listed in Table 1. In practice, these markers are least helpful when they are most needed (i.e., when anemia of inflammation is complicated by coexisting iron deficiency).[40] The main challenges to developing widely applicable algorithms that would assess the contribution of iron deficiency in anemia of inflammation include the heterogeneity of the underlying diseases, the variable relative severity of the components of inflammation and iron deficiency, and the lack of a standard test for evaluating the performance of these markers individually or in combination. Historically, the absence of stainable iron in the bone marrow was used as a standard for the diagnosis of iron deficiency, but this test is inappropriately invasive in most situations and is subject to sampling problems and interpretation by pathologists.[41-43] It is therefore not useful in the large clinical studies that would be required for the development of a generally applicable diagnostic algorithm for detecting a clinically relevant contribution of iron deficiency in patients with anemia of inflammation.

A practical clinical solution to the challenge of diagnosing iron deficiency in patients with anemia of inflammation is to focus on the detection and specific diagnosis of any occult blood loss (most frequently gastrointestinal) and on any iatrogenic blood loss from procedures and blood sampling. A therapeutic trial of oral or intravenous iron can then be considered, depending on the urgency of iron replacement and any side effects of previous iron therapy, with the likely effects of iron on both the underlying disease process and the patient's overall well-being taken into account.

The absorption of oral iron is commonly impaired in diseases with systemic inflammation,[44] although during mild inflammation, this effect is counteracted by the iron absorption–promoting effect of iron deficiency.[45] In anemia of inflammation, oral iron administration is therefore less reliable than the parenteral route and results in slower correction of the iron deficit. By contrast, intravenous iron preparations have become safer to administer and can be very effective in anemia of inflammation mixed with iron deficiency.[32] One approach to intravenous iron therapy in patients with both disorders is to estimate the amount of iron that would be needed to fully

Table 1. Differences in Biomarkers of Iron Deficiency and Anemia of Inflammation.

Biomarker*	Iron Deficiency	Anemia of Inflammation
Mean corpuscular volume	Low	Normal
Mean corpuscular hemoglobin	Low	Normal
Reticulocyte hemoglobin content	Low	Normal
Percentage of hypochromic erythrocytes	High	Low
Serum transferrin	High	Low
Serum transferrin receptor	High	Normal
Serum ferritin	Low	High
Serum hepcidin	Low	High

* Intermediate biomarker values would be expected when both iron deficiency and anemia of inflammation are present.

correct the anemia if it were caused solely by iron deficiency and administer half this amount. A useful and easy-to-remember formula for this estimate is as follows: iron (in milligrams)=hemoglobin deficit (in grams per deciliter)×body weight (in pounds [convert kilograms to pounds by multiplying by 2.2]). Partial hemoglobin correction typically occurs within 4 weeks after treatment with intravenous iron and levels off by 8 weeks, but patients may notice subjective improvement much earlier. For one-time treatment, all currently available intravenous iron preparations are similarly safe and effective, so the specific preparation and schedule of administration should be chosen on the basis of convenience for the patient and total cost.[46]

With respect to the potential effects of iron replacement on the underlying disease process, active infection, especially with gram-negative bacteria, is of particular concern because of evidence from an animal model[22] and clinical data[47] that implicate iron excess in the form of non-transferrin-bound iron as an enhancer of microbial pathogenicity. Indiscriminate iron supplementation may increase morbidity and mortality in low-resource settings where infections are endemic and nutritional deficiencies are widespread.[48]

TREATMENT

Treatments that target the infectious or inflammatory processes that cause anemia of inflammation will not only ameliorate the anemia but also

improve many symptoms and deficits caused by the primary disease. Such treatments are therefore more likely than treatments aimed solely at anemia of inflammation to yield a meaningful improvement for the patient. With such treatments, anemia can be mitigated remarkably rapidly, as documented in patients with Castleman's disease after treatment with anti–interleukin-6 antibody,[49] patients with giant-cell arteritis after treatment with glucocorticoids,[50] and patients with rheumatoid arthritis who received anti–interleukin-6 or anti–TNF-α therapy,[51] with clinically significant increases in hemoglobin seen after 2 weeks of treatment. In patients with anemic tuberculosis, use of antimicrobial agents completely resolved the anemia in about a third of the patients after 1 month of treatment and in about half the patients after 2 months of treatment.[52]

Unfortunately, effective treatment of the underlying inflammation is not always feasible. As specific treatment options for anemia of inflammation, erythropoietin derivatives, with or without intravenous iron, have been developed and tested predominantly in patients with chronic kidney disease. In addition to the effects of inflammation, such patients often have impairment in the expected anemia-stimulated increase in renal production of erythropoietin. Although there have been few specific clinical studies of the mechanism of action of erythropoietin derivatives combined with intravenous iron,[53] the combined drugs are expected to counteract the iron-restrictive effect of inflammation, as well as the associated resistance to endogenous erythropoietin.

A systematic review of the treatment of anemia with erythropoietin derivatives in patients with chronic kidney disease who did not require renal-replacement therapy showed a marked improvement in blood hemoglobin levels and some improvement in anemia-related symptoms. However, there was no measurable effect on the risk of disease progression requiring renal-replacement therapy.[54] The risks (chiefly treatment-related stroke) and some potential benefits of treatment with darbopoetin for patients with chronic kidney disease and relatively mild anemia (similar in severity to anemia of inflammation) were recently analyzed and carefully considered.[55] The authors concluded that treatment with darbopoetin is probably not advisable for

mild anemia in such patients but may be warranted for more severe anemia (hemoglobin level, <10 g per deciliter). The use of these treatment approaches in patients with anemia of inflammation who do not have chronic kidney disease has been studied only in a very limited manner,[56] and the disease-specific risks and benefits of erythropoietin therapy remain uncertain.

In view of these limitations, the treatment of anemia of inflammation with erythropoietin, with or without intravenous iron, in patients who do not have chronic kidney disease should be considered on an individual basis, with the benefits that would be meaningful to the patient carefully weighed against the documented risks of these interventions, as defined in the studies involving patients with chronic kidney disease not requiring dialysis. As an example, consider two patients, both with a hemoglobin level of 8.5 g per deciliter. The patient who is hospitalized with multiorgan manifestations of systemic vasculitis and urinary catheter–associated infection is easier to treat for anemia but much less likely to benefit meaningfully from the correction of anemia than the patient who is a working mother of two children and is receiving partially effective therapy for inflammatory bowel disease.

New compounds for the specific treatment of anemia of inflammation are under development. The targeted mechanisms are designed to reverse hypoferremia in anemia of inflammation by decreasing the level of hepcidin with the use of hepcidin binders or by hindering the access of hepcidin to its target ferroportin or antagonizing the signaling pathways that stimulate hepcidin production during inflammation (Table 2). Prolyl hydroxylase inhibitors stimulate the production of erythropoietin but may also act directly on the intestinal mucosa to increase iron absorption and thereby ameliorate iron restriction.

CONTRIBUTION OF ANEMIA OF INFLAMMATION TO ADVERSE OUTCOMES

In Lifelines, a very large, prospective cohort study, anemia of inflammation in older patients (>60 years of age) was associated with decreased survival and impaired health-related quality of life, most prominently, impaired physical functioning.[70] However, such studies cannot determine whether anemia of inflammation is merely

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])‡

* ACVR1 denotes activin A receptor 1, BMP bone morphogenetic protein, HIF hypoxia-inducible factor, and JAK1 and JAK2 Janus kinase 1 and 2, respectively.
† The phase 3 study involved patients with myelofibrosis.
‡ The phase 2 study involved patients with chronic kidney disease.

a marker of adverse outcomes or significantly contributes to them.[71] In principle, the contribution of anemia of inflammation to adverse outcomes can be ascertained only when highly specific and safe treatments for the disorder become available for clinical trials.

SUMMARY

Anemia of inflammation is a highly prevalent syndrome associated with systemic inflammation. In its most common form, anemia of inflammation is readily diagnosed as a normocytic, normochromic anemia associated with low transferrin saturation but a high serum ferritin level. With currently available treatment approaches, therapeutic measures directed at the underlying disease are most likely to result in improved outcomes that are meaningful to patients. An increased understanding of the pathogenesis of anemia of inflammation has stimulated the ongoing development of targeted therapies that may offer additional treatment options in the future.

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