To Treat 'Anemia of Inflammation,' First Manage the Underlying Disease

BY MIRIAM E. TUCKER
Senior Writer

BALTIMORE — A new understanding of the "anemia of inflammation" may help point the way to new treatments in the future, but in the meantime it illustrates why iron supplementation does not raise hemoglobin levels in patients with rheumatoid arthritis and other inflammatory diseases, Dr. Joan Bathon said at a conference on rheumatic diseases sponsored by the Johns Hopkins University.

Formerly known as "anemia of chronic diseases" because it is commonly seen in inflammatory diseases such as rheumatoid arthritis (RA) as well as in chronic infections and some cancers, the condition is now known by the term "anemia of inflammation," which better reflects its etiology. It is not the result of bleeding, hemolysis, nutritional deficit (vitamin B_{12}, folate, iron), or a marrow disorder, said Dr. Bathon, professor of medicine at Johns Hopkins, Baltimore.

Simply addressing the cause of the underlying inflammation—whether it is rheumatoid arthritis or infection—may be enough to correct the anemia.

Lacking an understanding of the underlying etiology, health care providers will often give these patients iron supplementation. However, "we know that iron treatment does not really alleviate this anemia," she said.

Anemia is extremely common among RA patients. In a study comparing 2,120 consecutive RA patients (contributing 26,221 hemoglobin determinations) with 3,843 patients who had noninflammatory rheumatic disorders (7,251 hemoglobin determinations) seen between 1974 and 2004 in a clinical practice setting, the prevalence of chronic anemia was 35.3% when a hemoglobin cutoff of less than 12 g/dL was used.

Hemoglobin levels were consistently lower among the RA patients than among those with noninflammatory conditions, by a mean of 0.8 g/dL.

Those data, reported at the 2005 American College of Rheumatology meeting by Dr. Frederick Wolfe of the National Data Bank for Rheumatic Diseases, Wichita, Kan., suggest that "more than one-third of patients with RA are anemic, if you use a broad definition," according to Dr. Bathon.

That study also found that among the RA patients, lower hemoglobin was associated with high disease activity; C-reactive protein levels were strongly predictive of anemia; and quality of life was reduced by 5.5% among the patients with anemia after adjustment for age and gender.

In general, patients with anemia of inflammation have decreased total circulating iron levels and binding capacity, yet their total body iron (ferritin) stores are increased.

At the same time, erythropoietin production is blunted, as is the response to endogenous erythropoietin. Red blood cell survival is modestly decreased. "Exogenous iron and/or exogenous erythropoietin do not fully resolve the anemia," she said.

Although iron is essential for oxygen transport and other vital functions, it also generates free radicals that can lead to oxidative damage, manifesting in conditions such as atherosclerosis, diabetes, or cancer.

But humans can't eliminate excess iron. Therefore, uptake from the gastrointestinal tract is tightly regulated and efficiently recycled. "No matter how much you give orally, there's only a limited amount the body can pick up," Dr. Bathon explained.

Recently, a small peptide hormone called hepcidin was identified as the principal regulator of systemic iron homeostasis. Synthesized in the liver, hepcidin inhibits the intestinal absorption of iron and suppresses release of iron from macrophage and hepatocyte stores.

Measurement of hepcidin levels is now being investigated as a possible diagnostic tool for various iron disorders. In one study, a novel urine hepcidin assay using mass spectrometry was able to discriminate among patients with secondary iron overload, iron-deficient anemia, and hereditary hemochromatosis (Blood 2005;106:3268-70).

Hepcidin production would be expected to be increased in RA patients, but that hasn't been studied, Dr. Bathon said.

Other data suggest that interleukin-6—but not interleukin-1 (IL-1) or tumor necrosis factor–α (TNF-α)—promotes anemia of inflammation by synthesizing hepcidin (J. Clin. Invest. 2004;113:1271-6), and some investigators have suggested that an antibody directed against IL-6 might therefore offer potential treatment for inflammation-induced anemia (Ann. Rheum. Dis. 2000;59 [Suppl. 1]:i21-7).

But, even though TNF-α and IL-1 don't induce hepcidin in some models, it's not clear whether the process is entirely mediated by IL-6.

In fact, treatment of RA patients with TNF-α blockers often does improve their anemia. It's not yet clear which treatment would be a better method—inhibition of IL-6 or TNF—for resolving anemia inflammation, Dr. Bathon said.

The role of erythropoietin for treating anemia of inflammation is also currently unclear. Although the response to exogenous erythropoietin tends to be blunted in RA patients in proportion to the severity of their inflammation, data from a few small studies do suggest that the treatment may nonetheless be beneficial by lessening their anemia.

One such study, involving 17 patients who received a total 32 weeks of treatment, showed an overall excellent hematologic response without toxicity but with no meaningful change in rheumatologic clinical status (Am. J. Med. 1990;89:161-8).

More recently, 30 patients with RA and anemia were treated with 150 IU/kg recombinant human erythropoietin twice weekly for 12 weeks, along with 200 mg of intravenous iron sucrose per week in the 23 patients who developed functional iron deficiency.

Average hemoglobin increased from 10.7 to 13.2 g/dL after a mean treatment period of 8 weeks. With recombinant human erythrpoietin treatment, patients also experienced increased muscle strength, decreased fatigue, fewer swollen or tender joints, and other improvements in disease activity variables (J. Rheumatol. 2001;28:2430-6).

But, Dr. Bathon said in an interview with RHEUMATOLOGY NEWS, erythropoietin "hasn't been studied enough to provide guidelines for its use, except perhaps prior to surgery where a lot of bleeding is anticipated."

Moreover, "it's kind of fallen by the wayside," in large part because "treatment of RA largely resolves the anemia."

Indeed, it may simply be that addressing the cause of the underlying inflammation—in RA, infections, or other chronic conditions—will correct its accompanying anemia as well. ■

When the First Anti-TNF-α Fails, Try Again

BIRMINGHAM, ENGLAND — Nearly half of all patients who initially failed therapy with anti–tumor necrosis factor–α agents benefited following a switch to a second or third drug in the class, according to a study presented at the annual meeting of the British Society for Rheumatology.

Dr. Jemma Pringle and associates studied 153 rheumatology patients who had a mean disease duration of 12 years upon entrance to a registry between 2001 and 2006. The patients' median initial disease activity score (DAS) was 7.55.

Of seven participants who switched to a third drug, four responded and took the drug for 6 months, with a 44% mean DAS decrease.

A cohort of 53 patients stopped their initial anti-TNF-α agent. Of these, 23 stopped due to an adverse event and 30 from loss of efficacy. Of the 33 who received a second anti-TNF-α agent, 22 responded and have remained on the drug for a median of 19 months at the time of her presentation, Dr. Pringle said.

The other 11 stopped anti-TNF-α therapy because of side effects and/or a lack of efficacy. Patients experienced a mean decrease in DAS of 32% from baseline to 4.15 after they undertook treatment with an alternative anti-TNF-α agent.

Of the seven participants who eventually switched to a third drug, four responded and continued to take the drug for a median of 6 months. There was a 44% mean decrease in baseline DAS among these patients.

"Nearly half of these are presently continuing their second or third agent with a clinically significant response," said Dr. Pringle, a rheumatologist at Gartnavel General Hospital, Glasgow, Scotland.

Up to 40% of patients do not respond to their initial anti-TNF-α drug, commented Dr. Pringle.

However, because each of the different anti-TNF-α agents have different properties, Dr. Pringle advised sticking with the class before considering other therapies, despite the fact that switching patients to a second anti-TNF-α agent is not as cost effective (since second response rates are lower), as one meeting attendee pointed out.

—Damian McNamara

RA Erosion Persisted

Swelling *from page 1*

showed no change in clinical swelling at follow-up, only 8 had swelling present at both baseline and follow-up. Swelling was absent at baseline in the other 108 joints.

Among the 133 joints in which swelling improved from baseline to follow-up, only 15 still had swelling at follow-up. The remaining 118 joints did not show any signs of swelling.

The relationship between repair and swelling for each joint in the study was statistically independent of any correlation between joints within a single patient.

The investigators found the same relationship between repair and swelling when they examined changes in joint-space narrowing rather than changes in erosion.

The results also indicated that the progression of erosion mostly occurs in individual joints with positive erosion change scores and persistent or worsening swelling.

Previous clinical studies have not validated whether traditional radiographic scoring methods of assessing rheumatoid arthritis damage can be applied at the level of a single joint to determine which individual joints are most likely to undergo repair.

Direct evidence of repair of individual joints within a patient can be obtained through sequential biopsies, but this method is impractical, in part because there is a strong possibility of missing individual repaired joints.

Few treated patients have an overall negative erosion change score (which indicates repair) after radiographic assessment of their joints. Only 3%-10% of patients in the TEMPO trial showed radiographic repair. ■