'Anemia of Inflammation' Explains Iron Issues in RA

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 doesn't 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.

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," Dr. Bathon said.

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. ■

Deficit of Vitamin D, Dark Skin Underlie Reemergence of Rickets

BY PATRICE WENDLING
Chicago Bureau

NEW ORLEANS — Nutritional rickets caused by vitamin D deficiency persists, in part because the risk factors may not be fully appreciated, Dr. Arlette Soros and colleagues reported in a poster at the Southern regional meeting of the American Federation for Medical Research.

They have encountered nearly a dozen cases in the last decade at Children's Hospital in New Orleans, and have documented four representative cases. The children, aged 3 months to 3 years, shared similar risk factors of having been breast-fed without any vitamin D supplementation, limited sun exposure, and darker skin.

Breast milk typically contains a vitamin D concentration of 25 IU or less per liter, which falls far short of the daily recommended minimum intake of 200 IU per day for infants, said Dr. Soros, a pediatrician with the division of endocrinology at Louisiana State University, New Orleans.

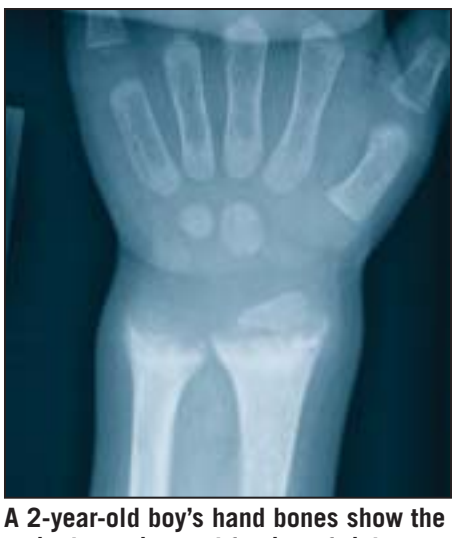
"It's wrong to think that a baby will get all the nutrients it needs from breast milk, and not give vitamin D supplementation" she said in an interview. "They may appear healthy, but there is a deficiency going on."

In addition, synthesis of vitamin D from ultraviolet sunlight is decreased in darker skin pigmentation.

Three of the children were African American, and one was Arabic. They presented with tetany, bony deformities such as bowed legs, widening of wrists and ankles, and rachitic rosary.

All of the children had low serum total calcium (range 6.1-7.8 mg/dL) and ionized calcium levels (range 2.2- 4.3 mg/dL); relatively low normal serum phosphorus levels (range 4.3-6.1 mg/dL), and elevated alkaline phosphatase levels (range 391-1,158 U/L). They also had low serum 25-hydroxy vitamin D (range 5.0-21 ng/mL), high parathyroid hormone levels (range 143-454 pg/mL), and relatively high 1,25-dihydroxy vitamin D levels (range 93-195 pg/mL). Renal and liver functions were normal.

After a single dose of intravenous calcium, ergocalciferol, or calcitriol, all of the children had complete or near-complete resolution of their symptoms. "[One boy] was up running the next day," Dr. Soros said. "This is very preventable." ■



A 2-year-old boy's hand bones show the typical cupping and fraying of rickets.

A year later, this shows his hands after vitamin D and calcium supplementation.

PHOTOS COURTESY DR. ALFONSO VARGAS/CHILDREN'S HOSPITAL

Study Affirms Safety of Long-Term Etanercept Use in JRA

BY JEFF EVANS
Senior Writer

Etanercept appears to maintain its safety through 8 years of continuous use in children with polyarticular-course juvenile rheumatoid arthritis without any incidence of cancers or serious opportunistic infections.

That is the conclusion reached by investigators of a multicenter, randomized, controlled trial that was later extended into an open-label study that specifically examined the long-term safety of the anti–tumor necrosis factor–α drug.

"Etanercept [Enbrel] was the first of the anti-TNF agents tested in children with JRA, and thus we have the longest and most clinical experience with it. This study, although small, was very reassuring," said Dr. Daniel Lovell of the Cincinnati Children's Hospital Medical Center, in an interview.

It is indicated for reducing the signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis (JRA) in those who have had an inadequate response to one or more disease-modifying antirheumatic drugs.

Of 69 patients who were originally randomized into the trial, Dr. Lovell and Dr. Andreas Reiff and their colleagues followed 58 patients into the open-label extension; all the patients had taken at least one dose of etanercept. Dr. Reiff originally presented the follow-up data at the annual European Congress of Rheumatology in Barcelona.

All children should be tested for varicella antibodies before starting treatment with etanercept.

DR. LOVELL

In the original randomized trial, all of the patients initially received etanercept for 3 months. Those who responded to the drug remained in the study and were randomized to either etanercept or placebo. Corticosteroids and anti-inflammatory drugs were allowed during both the randomized trial and the open-label extension, but relatively few patients were allowed to begin taking methotrexate again, said Dr. Reiff, head of the division of rheumatology and rehabilitation at Children's Hospital Los Angeles.

In the ongoing safety study, 42 of the original patients (61%) received at least 4 years of etanercept, and 16 (23%) received at least 8 continuous years of the study drug. They used the recommended dosage on the label of the subcutaneous injection formulation (0.4 mg/kg twice a week).

Overall, 16 patients (23%) reported adverse events. Long-term use did not significantly increase the rate of adverse events. Between years 4 to 8 of the follow-up period, only one severe adverse event (pyelonephritis) occurred. No cases of lupus; demyelinating disorders; tuberculosis or other opportunistic infections; or malignancy were reported. No deaths were reported.

Three cases of varicella infection occurred during follow-up, said Dr. Reiff. Although Dr. Lovell said that overall etanercept had a very good safety profile, he expressed caution about an increased risk of varicella in children on etanercept who lack protective antibodies to this virus.

Dr. Lovell suggested all children be tested for varicella antibodies before starting treatment with etanercept and that extra precautions be taken to avoid exposing nonimmune children taking etanercept to others with active varicella disease.

Dr. Reiff serves as an adviser and speaker for Amgen Inc. and Wyeth, which comarket etanercept in North America. ■