

ANEMIA ALERT



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Anemia Alert is NAAC's monthly e-newsletter for medical professionals. Each issue contains anemia news, expert commentary, feature articles and other recently updated content from www.anemia.org.

Regulating Iron in Chronic Disease

Maintaining healthy iron levels is an important step in anemia management, but standard iron tests do not always tell the full story in the presence of chronic inflammation. That's where the discovery of hepcidin, an important regulator of iron metabolism, may be just what the doctor ordered.

To help explain what this regulator could mean for your practice, NAAC is featuring **The Emerging Role of Hepcidin** in this month's issue of *Anemia Alert*. Also be sure to check out the newly approved IV iron drug, a recent Ask the Expert question on measuring hemojuvelin, and a review of a meta-analysis study on ESAs used to treat chemotherapy-induced anemia.

[The Emerging Role of Hepcidin in Iron Metabolism](#)



Research in recent years has increased knowledge about hepcidin and its integrated role in the absorption and movement of iron in the body – a breakthrough which has started to provide a more functional view of iron metabolism. Further understanding of how it inhibits the movement of iron and is itself regulated may eventually help clinicians better evaluate a patient's iron status and may assist in more effective, efficient treatment for anemia of chronic disease. Some potential advancements include:

- Early detection of iron deficiency in infants
- Identifying patients with anemia of chronic disease who are nonresponsive to ESAs
- Discovering patients who will require IV iron before oral iron proves ineffective

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Anemia in the News

[New Intravenous Iron Therapy, Ferumoxytol, Approved by FDA](#)

The Food and Drug Administration approved the market release of ferumoxytol, an intravenous iron therapy to treat iron deficiency in adult patients with chronic kidney disease either on or off dialysis. Ferumoxytol will be marketed under the name Feraheme™ and will be distributed starting the second half of July 2009. [Read the Full News Item](#)

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Ask the NAAC Experts

Measuring Hemojuvelin to Diagnose Anemia of Chronic Disease

Question:

In the presence of inflammation, would it make sense to analyze the soluble hemojuvelin concentration in the blood of patients at-risk for developing anemia of chronic disease to get a more rapid anemia diagnosis?

NAAC Expert Answer:

Yes, measuring soluble hemojuvelin concentrations could, in principle, help diagnose anemia of chronic disease, because in the presence of inflammation hepcidin levels are elevated and hemojuvelin levels are suppressed. A ratio of the two measurements would respond dramatically to inflammation associated with chronic disease. The data showing that hemojuvelin is suppressed by inflammation was obtained in mice, using hemojuvelin mRNA studies by qRT-PCR.¹ So far it has proven difficult to measure soluble hemojuvelin in blood reliably, but as soon as a sufficiently sensitive method exists, measuring hemojuvelin to diagnose anemia of chronic disease could be tested in humans.



References

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Research Reviews of Recent Clinical Trials

Meta-analysis of Darbepoetin Alfa Use in Patients with CIA

The use of erythropoiesis-stimulating agents (ESAs) in clinical trials has been shown to be an effective means of increasing hemoglobin (Hb) concentrations and reducing the need for red blood cell transfusions in patients with chemotherapy-induced anemia (CIA). Despite these findings, other recent trials have pointed to potential adverse events with ESA use, including an increased risk of mortality and disease progression. In fact, these trials spurred a black box warning on ESA labels by the Food and Drug Administration in 2007. Therefore, to reevaluate the benefits and risks of ESAs in clinical settings, Ludwig et al conducted the first pooled analysis of all randomized, placebo-controlled trials that involved the ESA darbepoetin alfa (DA).

This analysis included six studies and 2,122 patients with CIA, with lung and hematologic cancers being the most frequent primary tumor type. Of the total patient population analyzed, 1,200 patients received DA and 912 received a placebo. The study examined the following safety end points: overall survival, progression-free survival, and disease progression. According to statistical analysis, DA did not increase mortality or have any effect on disease progression, irrespective of baseline Hb levels. In addition, DA treatment was found to decrease the need for transfusion, an important finding that reaffirms the benefit of ESA use because, in this study, patients receiving transfusions were at a higher risk for mortality and adverse events.

This authors conclude that these results reaffirm the value of ESAs in clinical settings, and also suggests further reasons why other trials have shown contradictory results. For one, these studies have primarily initiated ESA therapy at higher Hb baselines and targeted higher overall Hb levels, which has been shown to be associated with adverse events. Patients who do not respond well to ESAs often have higher target Hb levels, and therefore may not represent an accurate outcome of ESA treatment. Also, patients undergoing transfusion typically have other, underlying health problems that could contribute to adverse events and confound the positive effects of ESA treatment. However, the authors contend that until the risks and benefits of ESA use are better understood, health care providers should continue to follow prescribing information and to administer ESAs cautiously according to patient need.

Ludwig H, Crawford J, Osterborg A, Vansteenkiste J, Henry DH, Fleishman A, Bridges K,

Glaspay JA. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. J Clin Oncol. 2009 Jun 10;27(17):2838-47.

NAAC Expert Commentary

In patients undergoing treatment for cancer, recent studies suggest an increased risk of death for patients treated with erythropoiesis-stimulating agents (ESAs) used in the treatment of anemia. This risk was confirmed by two meta-analyses.^{1,2} In the present study, Ludwig et al performed a meta-analysis of six randomized, controlled studies of darbepoetin alfa (DA) in patients receiving chemotherapy. They reached two important conclusions:

1. Darbepoetin alfa was associated with increased risk of thromboembolic complication
2. Darbepoetin alfa was not associated with increased risk of death or tumor progression

These findings may certainly bring some comfort to practitioners facing the devastating effects of anemia in cancer patients, because they conclusively demonstrated that DA does not seem to alter the natural course of cancer in the majority of patients receiving chemotherapy and because it can be safely administered to these patients with a Hb level up to 12 g/dL.

Nonetheless, it is important to identify some problems within the study. Firstly, the study did not include patients receiving the other ESA (epoetin alfa) and no explanation was provided by the authors. Whether these patients were not included because the authors did not have access to the data or because the use of epoetin alfa would have increased mortality rate, the reader is entitled to an explanation. Secondly, as the authors themselves state, time to progression (TTP) was an end point in only one of the 6 studies. In the other five studies, the TTP was deduced from clinical data. Thus, some small differences in TTP might have been missed.

Despite these limitations, the study clearly indicates that the risk of ESA use in patients receiving chemotherapy has been overemphasized and that it may be the appropriate time to reassess the issue.

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