Infliximab May Improve RA-Associated Anemia

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WASHINGTON — Among the clinical benefits associated with tumor necrosis factor–α inhibition in patients with rheumatoid arthritis are improvements in hemoglobin levels, Dr. Mittie Doyle said in a poster session at the annual meeting of the American College of Rheumatology.

Anemia associated with chronic inflammation is common in rheumatoid arthritis (RA), with an estimated prevalence of 50%, and contributes to the fatigue and impaired quality of life associated with the disease.

Some evidence suggests that the proinflammatory cytokine TNF-α has an inhibitory effect on erythropoiesis in chronic inflammatory disease, according to Dr. Doyle. Therefore, to determine if blocking TNF-α would improve hemoglobin levels, a post hoc analysis of data from three randomized trials was undertaken.

In ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis With Concomitant Therapy), 428 patients with active RA despite methotrexate therapy got either placebo or infliximab (3 or 10 mg/kg) at weeks 0, 2, and 6, and every 4 or 8 weeks thereafter.

In ASPIRE (Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset), 1,049 methotrexate-naive patients with RA of 3 years' duration or less received methotrexate and placebo, or methotrexate and infliximab (3 or 6 mg/kg) at weeks 0, 2, and 6 and every 8 weeks thereafter, reported Dr. Doyle.

In START (Safety Trial for Rheumatoid Arthritis With Remicade Therapy), 1,084 patients receiving methotrexate were randomized to one of three regimens: placebo through week 14 followed by infliximab (3 mg/kg) at weeks 22, 26, 30, 38, and 46; infliximab (3 mg/kg) at weeks 0, 2, and 6 and every 8 weeks through week 48, with dosage escalations up to 9 mg/kg permitted after week 22; or infliximab (10 mg/kg) at weeks 0, 2, and 6 and every 8 weeks through week 48.

Anemia was defined as hemoglobin below 12 g/dL and improvement as an increase in hemoglobin of 1 g/dL or more.

In all three studies, the proportion of patients with improvements in anemia was greater among the infliximab plus methotrexate groups than among the methotrexate plus placebo groups, according to Dr. Doyle of Centocor Research and Development Inc., Horsham, Pa.

In ATTRACT, 35.6% of patients receiving infliximab had an increase in hemoglobin of 1 g/dL or more by week 22, compared with 7.1% of those receiving placebo plus methotrexate.

In ASPIRE, 45.4% and 45.9% of patients receiving infliximab 3 mg/kg and 6 mg/kg, respectively, showed an increase in hemoglobin of 1 g/dL or more by week 22. Among patients receiving placebo plus methotrexate, 29.7% patients showed this degree of improvement.

In START, 22.3% and 23.9% of patients receiving infliximab 3 mg/kg and 10 mg/kg, respectively, had an increase in hemoglobin of 1 g/dL or more by week 22, as did 7.2% of those receiving placebo plus methotrexate.

"The study showed that treatment with combination therapy with infliximab and methotrexate resulted in larger improvements in hemoglobin than treatment with methotrexate alone," coinvestigator Dr. Joan Bathon, professor of medicine and director of the arthritis center at Johns Hopkins University, Baltimore, said in an interview. "Whether these changes will translate into clinically meaningful results, remains to be determined."

The pathogenesis of anemia of chronic inflammation has been linked to the impaired delivery and use of iron by erythroid precursors, according to Dr. Doyle. Elevated levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and TNF-α, have been shown to play an important role in the development of anemia of chronic inflammation through mechanisms that include shortened red blood cell survival, enhanced apoptosis of marrow erythroid progenitors, and suppression of erythropoietin production.

More recently, hepcidin has been identified as the acute phase protein that may link iron metabolism and red blood cell production to the type II acute phase response. IL-6 is the primary mediator of hepcidin production, and TNF-α likely influences hepcidin production indirectly via IL-6 induction, said Dr. Doyle in an interview.

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