Editorial

Anemia of Chronic Disease in Patients with Rheumatoid Arthritis: Aspects of Prevalence, Outcome, Diagnosis, and the Effect of Treatment on Disease Activity

Anemia is not considered a major problem in rheumatoid arthritis (RA) by the vast majority of physicians. This statement is based on the fact that studies on anemia in RA are sparse, with few systemic reviews, and no extensive literature on its prevalence and effect on various clinical and functional outcomes, including morbidity, mortality, and quality of life.

In this issue of *The Journal*, Wolfe, *et al* report results on the prevalence of anemia in a large cohort of 2120 consecutive patients with RA[1]. All patients with RA seen for clinical care at the Wichita Arthritis Center were investigated, with attention to the role that sex, age, and renal function play on the development of anemia. The estimated lifetime prevalence of anemia (hemoglobin, Hb, < 12 g/dl) was 51%, 34% in men and 58% in women. At lower cutpoints (Hb < 11 g/dl) the prevalence is 20% in men and 33% in women. As well, age had an effect on occurrence of anemia. The prevalence was more frequent in younger and older women, with the highest hemoglobin levels in patients about 58 years of age. The estimated annual incidence of anemia for both sexes was 7.9%. Also, a relationship between renal function and anemia could be established. A drawback of the study is that no data are available related to the cause of the anemia. And no data could be found nor an explanation for the lowered creatinine clearance of about 10 ml/min in the patients with RA. But this study clearly illustrates that the majority of patients with RA will develop anemia during their disease, thus supporting the statement that more attention should be paid to the occurrence of anemia in our patients with RA. Moreover, the annual incidence of anemia is nearly 8%, and the lifetime prevalence of severe anemia (Hb < 10 mg/dl) is 13.7%.

Overall, anemia in RA is classified as an anemia of chronic disease (ACD). ACD is considered the most frequent cause of anemia in RA; however, iron deficiency due to gastrointestinal blood loss or a combination of both should be considered in patients with RA developing anemia. In various cross-sectional studies, ACD has been reported to be present in 30% to 70% of patients with RA[2-6], as confirmed by the data from Wolfe[1]. The anemia develops slowly during the first month of illness[6] and has been found to be associated with a higher degree of disease activity. ACD is usually mild and nonprogressive, characterized by decreased plasma iron, decreased total iron-binding capacity, decreased iron saturation of transferrin, decreased bone marrow sideroblast, and normal or increased reticuloendothelial iron[7].

The diagnosis of ACD is made by exclusion. The main problem in differential diagnosis of ACD in RA is the presence of concomitant iron deficiency. The most reliable characteristic for the detection of iron deficiency is stainable iron content in bone marrow aspirate[7,8]. Extensive studies have demonstrated that for daily clinical practice a combination of serological characteristics was able to make a differentiation between an ACD and iron deficiency. The presence of low serum ferritin (< 50 g/l) in combination with high transferrin levels (50 g/l) and decreased mean corpuscular volume (MCV) of erythrocytes (80 fl) results in 100% sensitivity and specificity for the detection of iron deficiency[9]. Recently, serum transferrin receptor levels were proposed as a sensitive characteristic for detection of iron deficiency[10,11]. In other words, patients with RA with anemia and with elevated serum ferritin level (> 50 g/l), excluding iron deficiency, will have an ACD. By using these characteristics, it is possible to avoid many invasive investigations (colonoscopy, gastroscopy, bone marrow aspiration). To date, however, these findings have not been applied.

Evidence suggests that increased production of inflammatory cytokines (tumor necrosis factor-α) is linked to a decrease erythropoietin response in the bone marrow, thereby leading to inadequate erythropoiesis (*ex vivo* experi-

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ments). As well, this inhibition could be partly reversed by increasing the concentration of erythropoietin[12]. Most of all, by treating RA patients with recombinant human erythropoietin (EPO) the suppression of erythropoiesis could be overcome[13]. Within 6 weeks a significant increase in hemoglobin levels was obtained in the RA patients treated with EPO. It was very surprising that sustained benefit was also apparent for RA disease activity. Of patients in the EPO group, 32% showed a Paulus 20% response, compared to 8% of the placebo treated patients. A beneficial effect was also observed on secondary disease activity characteristics for the number of swollen joints, pain score, and patient's global assessment of disease activity. These findings were confirmed by other studies[14]. Investigations related to the effect of anemia on quality of life also demonstrated significant improvements during treatment with erythropoietin[14,15].

These results suggest that anemia is associated with a negative impact on both RA symptoms and quality of life. Thus the question needs to be raised of why so little research on anemia-related outcomes has been conducted. This gap in the literature is strange because anemia is a common comorbidity in patients with RA. Additional large-scale studies on prevalence and anemia-related outcomes are needed to support the importance of anemia screening and treatment in RA.

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