Effect of Tocilizumab on Serum Hepcidin and Anemia Response in Patients with Rheumatoid Arthritis

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Many chronic inflammatory rheumatic diseases are complicated by hematologic abnormalities. Anemia is one of the most common hematologic abnormalities in patients with rheumaticologic diseases; it is the most common extra-articular manifestation of rheumatoid arthritis (RA) and was estimated to occur in 30% to 70% of patients in various studies [1,2]. However, the importance of anemia in patients with RA is frequently underestimated. There are two primary types of anemia in patients with RA: anemia of chronic disease (ACD) and iron deficiency anemia [3,4].

ACD is characterized by hypoferremia in the presence of adequate iron stores; however, the pathogenesis of ACD is not clear. Two major factors appear to be important: trapping of iron in macrophages, making it relatively unavailable for new hemoglobin synthesis; and inability of the morphologically normal marrow to increase erythropoiesis in response to the anemia [5]. Proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-10, and interferon γ, play important roles in RA-associated anemia and are likely to act directly on red cell precursors in the bone marrow [5]. Therefore, the treatment of RA with inhibitors of inflammatory cytokines has significant therapeutic implications for the treatment of anemia in the context of inflammation and abnormal iron metabolism.

In a previous issue of *The Journal of Rheumatic Disease*, Park et al. [6] described the activity of tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, in diminishing the level of inflammatory anemia by inhibiting hepcidin production in Korean patients with RA. Hepcidin (hepatic bacterial protein) is an acute phase reactant that is produced in the liver and in immunocompetent cells. It was initially identified as a urinary antimicrobial peptide. Further studies showed that hepcidin is a master regulator of iron homeostasis in humans and in other mammals [7]. It inhibits iron absorption in the small intestine and the release of recycled iron from macrophages, effectively decreasing iron delivery to maturing erythrocytes in the bone marrow (Figure 1) [8].

Hepcidin is abnormally high, such as during inflammation, and thus serum iron levels fall due to iron trapping within macrophages and liver cells, and due to decreased absorption of iron in the gut [9]. Inflammation and infection increase hepcidin synthesis. Macrophages are stimulated during the inflammatory process; the stimulation depends on the severity of the inflammation. Activated macrophages release a network of cytokines. Of these, IL-6 is an attractive target as a mediator of ACD because its production is increased in patients with RA. In fact, Song et al. [10] demonstrated that tocilizumab inhibited IL-6-induced hepcidin expression in hepatoma-derived cell lines, and it ameliorated ACD by inhibiting hepcidin production in Castleman’s disease. Likewise, tocilizumab plays the same role in RA-associated ACD. In animals, administration of tocilizumab to monkeys with collagen-induced arthritis rapidly improved anemia and induced a rapid but transient reduction in serum hepcidin. Hepcidin mRNA expression was more potently induced by serum from arthritic monkeys, and this was inhibited by administering tocilizumab [11]. Recent human studies showed that an increase in serum
hepcidin in patients with active RA was associated with an elevated level of serum IL-6 [12-14]. It has been reported that TNF-α blockers also improved anemia in patients with RA [15]. Moreover, the administration of a TNF-α blocker quickly reduced serum IL-6 levels in patients with RA [16]. However, TNF-α does not induce expression of hepcidin mRNA in liver cells [17]. Therefore, these data suggest that improvement of anemia by administering a TNF-α blocker occurs indirectly via the suppression of IL-6 production. However, the pathogenesis of RA-associated anemia is complex and multifactorial. Sometimes RA-associated anemia is caused by gastrointestinal blood loss associated with the use of non-steroidal anti-inflammatory drugs or by bone marrow suppression associated with the use of other immunosuppressants, such as methotrexate. Another problem is the fluctuation of diurnal hepcidin levels; hepcidin levels are lower in the morning and higher in the afternoon. In addition, assay sensitivity is related to the amount of iron introduced by the diet [9]. Therefore, a thorough study of patients with RA-associated anemia needs to be carried out in a large population-based prospective study, using meta-analysis to clarify the influence of other therapies on the pathogenesis of RA.

In this respect, the evidence provided by Park and colleagues [6] is of great significance to the design of future epidemiological and clinical studies.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**

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