Anti-interleukin 6 receptor antibody tocilizumab reduces the level of serum hepcidin in patients with multicentric Castleman’s disease

We report two cases of multicentric Castleman’s disease (MCD) whose serum hepcidin levels were rapidly down-regulated by administration of tocilizumab, an anti-interleukin 6 (IL-6) receptor antibody. Our results indicate that IL-6-induced hepcidin over-production may be involved in the pathophysiology of microcytic anemia commonly observed in this disease.

MCD is a rare lymphoproliferative disorder with systemic manifestations, and over-production of IL-6 has been suggested to be a key event in its pathogenesis. Recently, tocilizumab (Chugai Pharmaceutical, Tokyo, Japan), which competitively blocks IL-6 binding to its receptor, has been successfully used to alleviate MCD symptoms. IL-6 up-regulates hepatic expression of hepcidin, a key regulator of iron metabolism by blocking the release of iron from macrophages and down-regulating iron uptake from the intestine. We monitored the level of serum hepcidin-25, the major active form of hepcidin, in two MCD patients receiving their initial dose of tocilizumab at Kyoto University Hospital. Tocilizumab (8 mg/kg body weight) was administered intravenously at 2-week intervals. Serum hepcidin-25 was semi-quantitatively analyzed using SELDI-TOF mass-spectrometry as described previously. To compensate for variations in sample concentrations, serum profilings were normalized by total ion current using Biomarker Wizard (Ciphergen ProteinChip Software 3.1.1), and the peak intensity at 2,789 was shown as arbitrary unit (AU; the range in healthy volunteers was 0-25 AU). This study was approved by the Ethics Committee of Kyoto University Graduate School and the Faculty of Medicine. Written informed consent was obtained from each patient.

Case #1 was a 24 years old woman previously treated with corticosteroids for three years. On admission, her Hb was 4.5 g/dL, mean corpuscular volume (MCV) was 92.857-858 µm³, CRP was 14.6 mg/dL, serum iron was 9 µg/dL, ferritin was 327 ng/mL, and hepcidin was 345 µg/mL. In this case, tocilizumab rapidly down-regulated the serum hepcidin-25 level from 18 to 3 AU in Case #1 despite very high serum IL-6 levels. In Case #1, urine hepcidin levels were also applied to the hepcidin assay. Clear peaks corresponding to hepcidin-20 and -25 detected before tocilizumab administration disappeared after treatment (Figure 1).

Interestingly, the serum hepcidin level in Case #1 was lower than that in Case #2 despite the much higher serum IL-6 level in Case #1. This may reflect the complexity of the mechanisms regulating serum levels of hepcidin. IL-6 and other factors, such as body iron status and erythropoietic activity, could influence hepcidin expression.

Down-regulation of hepcidin by very severe anemia may have counteracted the effect of IL-6 on hepcidin pro-
duction in Case #1. After 3 months of tocilizumab treatment, Hb increased to 12.3 and 13.0 g/dL in cases #1 and #2 respectively. Our results indicate that inappropriate production of hepcidin, possibly related to the pathophysiology of microcytic anemia in MCD, can be reversed quickly by blocking the IL-6 pathway with tocilizumab.

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Funding: this work was supported in part by a grant-in-aid for scientific research from the Ministry of Education, Science, Sports and Culture of Japan and a grant from Takeda Science Foundation.

Key words: interleukin-6, Castleman’s disease, tocilizumab, iron metabolism, hepcidin.

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