Changes in the Plasma Level of Macrophage Migration Inhibitory Factor in Ulcerative Colitis Patients Treated with Selective Granulocyte and Monocyte Apheresis

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Ulcerative colitis (UC) is characterized by chronic and relapsing colitis and its pathogenesis is still unknown. In addition to conventional drug treatment such as 5-aminosalicylic acid and glucocorticoid, selective granulocyte and monocyte apheresis (GMA) with Adacolumn has been developed as a new tool for the treatment of UC (1, 2). GMA removes 65% of granulocytes, 55% of monocytes/macrophages, and a small fraction of lymphocytes from the blood in the column (1). However, the mechanism of the anti-inflammatory effect of GMA has not been fully elucidated. Macrophage migration inhibitory factor (MIF) is important in the regulation of the immune response and in the development of inflammation, including gastritis and colitis (3); the level of MIF is increased in the serum of UC patients (4). In this report, we investigated the effect of GMA on the circulating MIF level in patients with UC.

Six UC patients (age; 18-45, gender; 2 men and 4 women, duration of UC; 14-203 months) were enrolled in this study. In terms of disease distribution of UC, 4 patients had pancolitis, and 2 had left colon involvement. All patients were receiving oral prednisolone (12.5-30 mg/day) and 5-aminosalicylate (2250 mg/day) at the time of study. None of them received immunosuppressant. Clinical activity index (CAI) was scored by Rachmilewitz’s classification (5). A responder was defined as a patient with decrease in CAI ≥ 4. Each patient gave the informed consent. This study was approved by the Ethical Committee of Hokkaido University Hospital. The procedure for GMA was performed as

![Figure 1](image_url)

**Figure 1.** Changes in the scores of the clinical activity index (CAI) and the plasma levels of macrophage migration inhibitory factor (MIF) in the patients treated with GMA. The statistical significance of the differences between means were determined by the Wilcoxon signed-rank test. (a) Changes in the scores of CAI before the first session of the granulocyte and monocyte apheresis (GMA) therapy and after the final session of GMA therapy. Before: before the first session of GMA, After: after the final session of GMA. (b) Changes in the plasma MIF levels in pre- and post-GMA therapy at the first session. Pre: pre-GMA, Post: post-GMA. Samples from 6 patients were obtained during the first GMA procedure.

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previously described using Adacolumn (JIMRO, Takasaki, Japan) once a week for 5 or 10 weeks (1). Blood samples were obtained each time before and after GMA, and plasma MIF levels in the samples obtained were measured with MIF enzyme-linked immunosorbent assay (ELISA) kit (Sapporo Immunodiagnostic Laboratory, Sapporo, Japan) according to the manufacturer’s protocol. The results were expressed as means ± standard error (SE). The statistical differences in the CAI scores and the plasma MIF levels were analyzed by Wilcoxon signed-rank test. p<0.05 was considered statistically significant.

Four patients received 5 GMA sessions and 2 patients received 10. GMA procedures were well tolerated by all patients. After the final GMA session, all patients achieved clinical response (Fig. 1a). The average of CAI scores was significantly decreased after the final GMA session (before, 10.7±0.9 vs. after, 3.7±0.9; p=0.027). In the samples obtained at the first GMA session, GMA reduced the plasma levels of MIF in all patients (Fig. 1b). In the first GMA session, the average level of MIF in the patients was significantly decreased at post-GMA compared with pre-GMA (before, 6.8±1.0 ng/mL vs. after, 2.9±0.5 ng/mL; p=0.028). The results of the samples from the other GMA sessions were similar to those obtained from the first GMA session (2nd session: before, 9.9±2.0 ng/mL vs. after, 5.8±1.5 ng/mL; p=0.028, 3rd: before, 9.1±2.2 ng/mL vs. after, 5.2±0.9 ng/mL; p=0.046, 4th: before, 11.3±4.0 ng/mL vs. after, 6.8±2.9 ng/mL; p=0.046, 5th: before, 15.5±3.6 ng/mL vs. after, 7.1±2.9 ng/mL; p=0.028).

The mechanism of the anti-inflammatory effects of GMA remains unclear. The results of several investigations suggest that pro-inflammatory cytokines, including TNF-α, interleukin (IL)-1β, IL-6 and IL-8, are increased in UC patients and they are associated with the effects of GMA (1, 2). Consistent with these cytokines, the serum level of MIF was increased in UC patients (4). In the present study, we found that GMA significantly decreased the plasma level of MIF in all responders, suggesting that GMA removed immunocytes, such as monocytes and granulocytes, which highly secrete MIF. However, we did not analyze the leukocytes. Thus, we cannot confirm the association between effect of GMA on circulating MIF level and clinical effectiveness of GMA in patients with UC. Interestingly, the plasma levels of MIF were increased in the patients just before the next GMA session. Although the reason has not been clarified, it is suggested that the effect of GMA on the circulating level of MIF is transient.

Although further study is necessary to elucidate the effects of GMA on the expression and bioactivity of MIF, our data suggest that MIF is associated with the mechanism of the effects of GMA in UC.

References


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