学 位 論 文 の 要 旨

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学 位 論 文 名　Induction of Mucosal Healing by Intensive Granulocyte/Monocyte Adsorptive Apheresis (GMA) Without Use of Corticosteroids in Patients With Ulcerative Colitis – Long-term Remission Maintenance After Induction by GMA and Efficacy of GMA Re-treatment Upon Relapse

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論 文 内 容 の 要 旨

INTRODUCTION

Ulcerative colitis (UC) is characterized by chronic recurrent inflammation of the entire colon. Although 5-aminosalicylic acid (5-ASA) is initially given for active UC, should that fail, corticosteroids (CS) and immunosuppressants including biologics are initiated. During treatment, patients must be followed for opportunistic infections and other adverse effects. Granulocyte and monocyte adsorptive apheresis (GMA), an extracorporeal blood circulation method performed with the Adacolumn (JIMRO, Takasaki, Gunma, Japan), is used to selectively remove active granulocytes/monocytes from peripheral blood with few adverse effects. Currently, mucosal healing (MH) is considered to be the predominant factor for predicting disease relapse in UC cases. We previously found that intensive GMA (2x/week) without CS led to high rates of rapid clinical remission and mucosal healing (MH) in active UC cases. However, there are few reports of long-term prognosis of UC patients who achieved MH by GMA. In this study, the cumulative non-relapse survival rate was evaluated in UC patients who had achieved MH with first-time intensive GMA (first GMA) without CS as well as efficacy of GMA re-treatment (second-time intensive GMA, second GMA) without CS for relapsed UC during the maintenance period.

MATERIALS AND METHODS

Clinical records from Iseikai Hospital and Osaka Saiseikai Nakatsu Hospital of patients treated from April 2010 to April 2019 were used in this retrospective observational study. Ethics committees of both hospitals approved the protocol before the investigation was commenced.

Seventy-eight UC patients who had achieved clinical remission and MH under first GMA without CS were enrolled (38 males, 40 females; mean age 43.2±15.0 years). Clinical remission was defined as clinical activity index (CAI; Rachmilewitz index) score ≤4 points, while MH was defined as Mayo endoscopic score (MES) of 0 or 1. Each received oral maintenance with 5-ASA and/or thiopurine, and were observed until week 156. Disease relapse was diagnosed when a CAI score of >7 points was confirmed despite receiving the maximum dose of 5-ASA or adjusted dose of thiopurine. The cumulative non-relapse rate was calculated 26, 52, 104, and 156 weeks after achieving clinical remission and MH by first GMA. Clinical parameters were then compared between relapsed and non-relapsed patients to determine relapse-associated factors.

For relapsed UC cases, intensive second GMA without CS treatment was given using the same protocol as with first GMA, with primary efficacy evaluated based on clinical remission rates at 2, 4, and 6 weeks after starting second GMA (2x/week) in the same patients (week 6; one week after end of 10 sessions over five weeks). Secondary efficacy was assessed by comparing MES and MH rates at week 6. Adverse events were examined and recorded at each visit, and patients who achieved clinical remission with intensive GMA continued to be followed.

Data are presented as the mean ± SD. The cumulative non-relapsing survival rate was calculated using the Kaplan-Meier method. Categorical and continuous data were compared with those in other cases using a two-tailed Fisher's exact test, a chi-square test, or Student's *t*-test. Categorical and continuous data in the same cases were compared using a McNemar test or paired *t*-test. A p value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed with StatMate V (ATMS Co., Ltd., Tokyo, Japan).

RESULTS AND DISCUSSION

During the maintenance period, 34 patients had relapse. Overall cumulative non-relapse survival rates in those who achieved both clinical and endoscopic remission from first GMA at weeks 26, 52, 104, and 156 were 87.2%, 71.1%, 57.6%, and 56.4%, respectively. Relapse rate during maintenance was significantly lower in the MES 0 (28.6%; 8/28) than the MES 1 (52.0%; 26/50, p=0.045) group. Furthermore, mean MES before and after first GMA was significantly higher in patients with as compared to without relapse (before: 2.4±3.6 vs. 2.2±0.4, p=0.049; after: 0.8±0.4 vs. 0.5±0.5, p=0.046). There were no significant differences between the groups for age, gender, disease duration or extent, degree of CAI score, or maintenance medication.

Second GMA was performed for 34 UC relapse patients without use of CS. Clinical remission rates in association with first and second GMA were compared in the same patients. The clinical remission rates after second GMA were 32.4% and 50.0% at weeks 2 and 4, lower as compared to first GMA (50%, p=0.070, and 85.3%, p<0.001, respectively). That rate at week 6 (88.2%), one week after the end of second GMA, was not different from that at that same time period during the first GMA course (100%) (p=0.134). Furthermore, mean time to clinical remission in second GMA cases (27.9±16.8 days) was significantly greater than that during the first GMA course (21.2±12.7 days). Mean MES scores at week 6 were not different (0.9±0.9 vs. 0.8±0.4, p=0.423) and endoscopic remission rate at week 6 (100% vs. 84.8%; p=0.074) was also not significantly different. The rate of clinical and endoscopic remission (MES=0 or 1) at week 6 for first GMA was 100%, as patients who achieved clinical remission and MH with GMA were enrolled. No serious side effects were observed throughout the study term.

In the present study, MH by GMA without CS contributed to maintenance of long-term remission. The relapse rate during the maintenance period was significantly lower in the MES 0 as compared to the MES 1 group, suggesting that endoscopic activities before and after first GMA are possible predictors of relapse in UC patients who achieve clinical remission and MH with intensive GMA. Thus, gastroenterologists should keep the possibility of relapse even up to three years after GMA in mind, especially in cases with severe endoscopic findings before induction treatment and inflammation remaining after beginning treatment. Moreover, GMA retreatment following relapse was shown to induce clinical remission and MH.

There are few reports regarding GMA retreatment efficacy in relapsed UC patients. In the present cohort, all who relapsed during the maintenance period underwent second GMA without concomitant CS, of whom 88.2% again achieved clinical remission with no serious side effects. Also, there was no significant difference between the MES values obtained just prior to starting first and second GMA. However, second GMA clinical efficacy in relapsed UC patients developed more slowly than in first GMA cases. Nevertheless, despite slower response to second GMA, the majority of relapsed patients again achieved clinical remission without CS use. In this regard, GMA can be considered as a low tolerance immunosuppressive induction method for UC patients. Thus, GMA re-treatment is likely effective in patients who have suffered relapse.

CONCLUSION

MH induction by intensive GMA without use of CS in UC patients contributes to subsequent long-term clinical remission maintenance. GMA re-treatment efficacy was comparable to that of first GMA in the same patients who had relapse. Thus, to achieve MH in UC patients, intensive GMA prior to use of CS and biologics can be a suitable option.