Long-term clinical impact of early introduction of granulocyte and monocyte adsorptive apheresis in new onset, moderately active, extensive ulcerative colitis

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Abstract

Background and aims: The efficacy of granulocyte and monocyte adsorptive apheresis (GMA) for patients with a first episode of ulcerative colitis (UC) has been scarcely reported. This study was to see if the introduction of GMA at an early stage reduces corticosteroid administration and steroid dependency in the long term clinical course of UC.

Methods: Forty consecutive patients with moderately active symptoms as the first attack of UC were included. Twenty patients were treated with GMA, with or without corticosteroids (GMA group), and the other 20 were given corticosteroids without GMA (steroid group). All patients were monitored for 5 years. Relapses were treated in the same manner as the first attack in both groups. The total dose of steroid administered and the appearance of steroid-dependency were to be compared between the two groups.

Results: All patients in both groups achieved clinical remission after the first attack. The mean number of relapses per patient was 2.8 in the GMA group and 2.9 in the steroid group (P = 0.86). During this study, 5 patients in the GMA group did not require corticosteroids. The mean dose of steroid administered during the 5 years was 2141 mg in the GMA group vs 5443 mg in the steroid group (P = 0.002). One patient in the GMA group and 7 in the steroid group were steroid-dependent at the end of the study (P = 0.048).

Conclusions: In patients with the first UC episode, GMA therapy at an early stage significantly reduces steroid administration and steroid-dependency in the long-term clinical course.

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1. Introduction

Corticosteroids (prednisone, prednisolone, hydrocortisone, etc.) have been used for many years in the treatment of patients with moderate to severe ulcerative colitis (UC) or who fail to respond to optimal doses of 5-aminosalicylic acid (ASA) compounds.\(^1\)\(^-\)\(^3\) Corticosteroids are faster-acting than the 5-ASA compounds. Patients frequently experience improvement in their symptoms within days of starting corticosteroids. Once the symptoms are under control, the reduction can resume at a slower pace. Some patients become corticosteroid dependent.\(^4\)\(^-\)\(^6\) These patients consistently develop symptoms of colitis whenever the corticosteroid dose reaches below a certain level. Because corticosteroids are not useful in maintaining remission and because they have predictable and potentially serious side effects, these drugs should be used for the shortest possible length of time. In patients who are corticosteroid dependent or who are unresponsive to corticosteroids, other anti-inflammatory medications, immunomodulatory medications or surgery are considered.\(^1\)\(^-\)\(^3\)

Active UC is frequently associated with infiltration of large numbers of leukocytes (granulocytes and monocytes) into the intestinal mucosa. Removing activated leukocytes from the blood and modulating immune system components such as cytokines by apheresis have the potential to decrease inflammation in patients with UC. In Japan, since April 2000, granulocyte and monocyte adsorptive apheresis (GMA) has been approved by the Japan Ministry of Health and Welfare as one treatment option for active UC.\(^7\)\(^-\)\(^8\) Several clinical trials have shown that GMA is safe and effective for patients with active UC, and GMA has steroid-sparing efficacy.\(^9\)\(^-\)\(^13\)

In Japan, GMA is considered an effective alternative or addition to conventional medical therapy, and it has been used as an alternative therapy in patients with steroid-refractory or -dependent UC. Further, several studies found that GMA is more effective for steroid naïve patients.\(^14\)\(^-\)\(^17\) However, up to now, the efficacy of GMA for patients with a first episode of UC has been scarcely reported. This study was to assess whether early induction of GMA therapy reduces corticosteroid administration and steroid dependency in the long-term clinical course following the first attack of UC.

2. Patients and methods

2.1. Study design

This was a retrospective study with prospective data collection undertaken at the Yokkaichi Social Insurance Hospital, a referral centre treating a large number of patients with inflammatory bowel disease in the Mie Prefecture of Japan. The study was conducted in accordance with the principle of good clinical practice and the Declaration of Helsinki. Our study protocol was reviewed and approved by our institutional Review Board.

2.2. Patients

Patient inclusion criteria were: 1) age between 20 and 75; 2) had endoscopic and histologic diagnosis of UC, not having indeterminate colitis; 3) with endoscopic inflammation that extends proximal to the splenic flexure; 4) had moderately active symptoms (disease activity index [DAI]\(^18\) score of 6–9) as a first episode of UC; and 5) who failed to respond to optimal doses of 5-ASA compounds. Exclusion criteria for GMA therapy were: 1) patients with serious cerebral, pulmonary, cardiac, hepatic or renal disease; 2) had laboratory abnormalities like leukocyte count <2000/\(\text{mm}^3\) or haemoglobin <7.0 g/dL; and 3) had a known bleeding disorder or was receiving anticoagulant therapy other than for the GMA procedure. Between January 2003 and September 2006, 40 consecutive patients who met the inclusion criteria were entered into this study.

2.3. Treatment for the first episode

In our institution, since July 2004, GMA has been used for patients with the first episode of UC. In this trial, 20 patients entered before July 2004 were given corticosteroids without GMA (steroid group), and the other 20 patients thereafter entered were treated with GMA, with or without corticosteroids (GMA group).

In the steroid group, the dose of steroids for moderate active UC was determined in accord with the guidelines of the Japanese Ministry of Health, Labour and Welfare. Patients were given oral prednisolone 30–40 mg/day followed by tapering of 5–10 mg/week until 20 mg/day which was then followed by tapering at 2.5–5 mg/week in line with clinical improvement. Patients who did not respond to oral prednisolone 30–40 mg/day were treated with higher dose of prednisolone or intravenous administration of steroids.

In the GMA group, GMA therapy was done with the Adacolumn, which is an adsorptive carrier based granulocyte and monocyte apheresis device with a volume of 335 mL, filled with about 220 g cellulose acetate beads of 2 mm diameter as the column adsorptive carriers.\(^7\)\(^-\)\(^8\) During this study, GMA was administered weekly. GMA session time was 90 min/session, at 30 mL/min. Patients who achieved clinical improvement (a decrease in stool frequency or rectal bleeding) after 5 GMA sessions, but did not achieve clinical remission (normal stool frequency and no rectal bleeding) were given 5 additional GMA sessions. Corticosteroids (prednisolone 20–40 mg/day) were started for patients who had no initial response to GMA. Further, in case of worsening during GMA treatment, patients were given corticosteroids (prednisolone 20–40 mg/day). The dose of steroids was to be tapered or discontinued in line with clinical improvement during the GMA treatment.

2.4. Assessment of safety and efficacy

Adverse event experienced during and after treatment was recorded. As clinical symptoms, stool frequency, consistency, presence or absence of abdominal pain, tenesmus, rectal bleeding and mucus discharge were recorded daily. Stool frequency and rectal bleeding were scored according to the DAI system.\(^16\) Stool frequency score 0=normal number of stools; score 1=1–2 stools/day above normal; score 2=3–4 stools/day above normal; score 3=≥5 stools/day above normal; and rectal bleeding: score 0=no blood; score 1=streaks of blood with stools less than half of the time; score 2=obvious blood with stools most of the time;
score 3 = blood alone passed. Clinical remission was defined as normal stool frequency (=score 0) and no rectal bleeding (=score 0). Further, the dose of steroid administered and the appearance of steroid-dependency were recorded.

2.5. Follow-up

All patients were followed up for 5 years following the first UC attack. Patients who achieved clinical remission were given 5-ASA compounds as maintenance therapy. Patients who relapsed during the maintenance therapy were treated in the same manner as the first attack in both groups. Patients who did not respond to the GMA or corticosteroid therapy were treated with an increased dose of corticosteroids, immunosuppressants, or colectomy if necessary.

2.6. Outcome measures

Primary outcome measures included the total dose of steroid (prednisone) administered and the appearance of steroid-dependency during the 5-year observation period. Secondary outcome measure was the appearance of adverse events. These outcomes were compared between the two groups. In this study, steroid dependency is defined as patients respond to corticosteroids, but experience a loss of clinical response when corticosteroids are tapered to less than 10 to 30 mg/day, or a relapse within 3 months of stopping steroids.

2.7. Statistics

Comparison of frequencies was by using the chi-square test with Yates’ correction. Continuous data are presented as the mean±SE values. The mean values between two groups were compared by using the unpaired t-test. The cumulative proportion of patients in remission and patients without steroid-dependency was calculated by the Kaplan–Meier method, and was compared between the groups by using the log-rank test. P<0.05 was considered statistically significant.

3. Results

3.1. Baseline demography

Baseline characteristics of patients in both treatment groups are shown in Table 1. Patients were well matched with respect to age, sex, duration of symptoms before entry, DAI score, medications before entry, and extraintestinal manifestations.

3.2. Treatment outcomes

In the GMA group, 13 patients (65%) required concomitant corticosteroids, and the other 7 patients were treated with GMA alone in the management of the first episode (Table 2). The median time to start corticosteroids after the first GMA session was 2 weeks. Twelve patients (60%) received 5 GMA sessions, and 8 patients 10 GMA sessions. All patients in both treatment groups achieved clinical remission after the first attack of UC. The mean duration between initiation of treatment and achievement of remission was 3.9±0.3 weeks in the steroid group vs 6.4±0.5 weeks in the GMA group (P=0.0002). The mean dose of steroid (prednisone) administered between initiation of treatment and achievement of remission was 320±64 mg in the GMA group, which was significantly smaller than 834±26 mg in the steroid group (P<0.0001).

After induction of remission, 6 patients were treated with sulfasalazine and 14 patients with mesalazine in the steroid group vs 5 patients with sulfasalazine and 15 patients with mesalazine in the GMA group (P>0.99). The mean dose of sulfasalazine was 2.83±0.31 g/day in the steroid group vs 2.41±0.07 g/day in the GMA group (P=0.58). The mean dose of mesalazine was 2.14±0.07 g/day in the steroid group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Steroid group (n=20)</th>
<th>GMA group (n=20)</th>
<th>P</th>
</tr>
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<tr>
<td>Age at entry (mean±SE)</td>
<td>34±1.9 years</td>
<td>33±2.5 years</td>
<td>0.81</td>
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<tr>
<td>Male:female</td>
<td>13:7</td>
<td>12:8</td>
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<tr>
<td>Current smokers</td>
<td>4 (20%)</td>
<td>4 (20%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Duration of symptoms before entry (mean±SE)</td>
<td>19±1.7 weeks</td>
<td>20±2.1 weeks</td>
<td>0.66</td>
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<tr>
<td>DAI score at entry</td>
<td></td>
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<tr>
<td>Score 6</td>
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<td>4 (20%)</td>
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<td>Score 7</td>
<td>5 (25%)</td>
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<td>Score 8</td>
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<tr>
<td>Score 9</td>
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<td>4 (20%)</td>
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<tr>
<td>Mean±SE score</td>
<td>7.4±0.2</td>
<td>7.6±0.2</td>
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</table>

Table 2  Treatment for the first episode in the GMA group.

<table>
<thead>
<tr>
<th>Concomitant corticosteroids</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Prednisolone 20 mg/day</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Prednisolone 30 mg/day</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Prednisolone 40 mg/day</td>
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<tr>
<td>Mean±SE dose of prednisolone</td>
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<tr>
<td>Number of GMA sessions</td>
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<td>5</td>
<td>12 (60%)</td>
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<tr>
<td>10</td>
<td>8 (40%)</td>
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<tr>
<td>Mean±SE number of sessions</td>
<td>7±0.6</td>
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</table>
group vs 2.10±0.08 g/day in the GMA group (P=0.70). Seventeen patients (85%) in both groups experienced at least one relapse. The cumulative proportion of patients in remission after treatment for the first episode was compared between the groups (Fig. 1). There was no statistically significant difference between the groups.

The number of relapses experienced during this study in both groups is presented in Fig. 2. The mean number of relapses per patient was 2.8±0.4 in the GMA group vs 2.9±0.4 in the steroid group (P=0.86). When analyzing outcomes for all relapses which were successfully managed, the mean dose of steroid (prednisone) required per relapse before achieving remission was 417±51 mg in the GMA group, which was significantly smaller than 857±28 mg in the steroid group (P<0.0001).

During this study, 5 patients (25%) in the GMA group did not require corticosteroids. The mean dose of corticosteroid administered (per patient) for each observation year is presented in Fig. 3. In each year, the dose of the corticosteroid was significantly smaller in the GMA group than in the steroid group (all P<0.05). The mean dose of the corticosteroid administered over the 5-year observation period was 2141±454 mg in the GMA group, which was significantly smaller than 5443±856 mg in the steroid group (P=0.002). Nine patients (45%) in the steroid group and 4 patients (20%) in the GMA group were given azathioprine (25–150 mg/day) for maintaining remission (P=0.18). Three patients (15%) in the steroid group and 1 patient (5%) in the GMA group required colectomy due to lack of response to medical treatment (P=0.60).

### 3.3. Adverse events and steroid-dependency

Overall, 16 patients (80%) in the steroid group and 13 patients (65%) in the GMA group developed adverse events (P=0.48). Steroid-related adverse events developed in the 16 patients (80%) in the steroid group vs 8 patients (40%) in the GMA group (P=0.02). Thus, the incidence of adverse events related to steroids was significantly lower in the GMA group. Further, 1 patient (5%) in the GMA group and 7 (35%) in the steroid group were steroid-dependent at the end of this study (P=0.048). The cumulative proportion of patients without steroid-dependency was significantly higher in the GMA group (Fig. 4).

During the GMA therapy, 5 patients (25%) experienced adverse events during at least one GMA session. The most common adverse event during the GMA therapy was mild headache followed by feeling of fatigue and fever (37–38 °C). None of these adverse events related to GMA was serious, and all patients completed the GMA sessions according to the protocol.

### 4. Discussion

To our knowledge, this is the first study to evaluate the steroid sparing effect of GMA therapy for patients with a first episode of UC. We followed up patients for 5 years after the first attack to see if the introduction of GMA therapy at an early stage reduces steroid administration and steroid dependency in the long term clinical course of UC. In the management of the first episode, 65% of patients in the GMA group required concomitant steroid (prednisolone 20–40 mg/day), and 35% patients were treated with GMA alone. During the entire study, 25% of patients in the GMA group did not require steroid administration.
at week 12, 83% of patients in the GMA group vs 65% in the steroid group, but statistical significance was not attained. The cumulative amount of prednisolone received was significantly lower in the GMA group than in the steroid group, although the rate of steroid-free patients was not significant. GMA appeared to be an effective adjunct to standard drug therapy of moderately severe UC by promoting remission and sparing steroids.

In our previous study, we identified factors affecting clinical efficacy of GMA in patients with moderately or severely active UC. We found that the cumulative dose of prednisolone before entry was one of significant factors for clinical remission; the clinical remission rate was 78% in patients who were not receiving prednisolone (steroid naïve), 59% in patients with a total dose of >0 g and <5 g, and 17% in those with a total dose of ≥5 g. Another study reported that first UC episode and short disease duration were valuable predictors of response to GMA. Based on the outcomes of these studies, it appears that steroid naïve patients and patients on low dose steroid and short duration of exposure respond to GMA.

In the study by Faubion and colleagues, 63 patients with UC required corticosteroids to control their symptoms, and were followed up according to the immediate outcome (30 days) and the 1-year outcome. Immediate outcomes were complete remission in 34 patients (54%), partial remission in 19 (30%), and no response in 10 (16%). One-year outcomes were prolonged response in 31 (49%), corticosteroid dependence in 14 (22%), and operation in 18 (29%). Their study underlines that most patients with UC initially respond to steroids but already after 1 year a significant proportion lose the response; this leads to steroid-dependency or the need for surgery, even among those who initially responded to the treatment.

During our GMA therapy, none of the serious adverse events were observed. All patients completed their GMA treatment course without any problem. This study confirmed that GMA therapy is safe and well tolerated. Steroid-related adverse events more frequently developed in the steroid group, 80% vs 40% in the GMA group. The induction of GMA therapy could reduce the risk of steroid-related adverse events in the long term. Further, 5% of patients in the GMA group and 35% in the steroid group were steroid-dependent at the end of this study. The cumulative incidence of steroid-dependency was significantly reduced in the GMA group.

Immunosuppressants as a maintenance therapy were slightly different from Japan to the Western countries. Our results should be confirmed in a prospective randomised trial using an appropriate dose of steroids followed by early introduction of azathioprine in the steroid group when fulfilling steroid dependence criteria. In addition, the cost-effectiveness of GMA should be considered. When compared with corticosteroids, GMA is expensive; one treatment session costs approximately €800. However, if GMA

Figure 3 The mean dose of corticosteroid administered (per patient) for each observation year.

In both treatment groups, all patients achieved clinical remission albeit a quicker response in the steroid group. The dose of steroids required before achieving remission was significantly smaller in the GMA group. The majority of patients in both groups experienced relapse during the 5-year observation period. There was no significant difference in the cumulative proportion of patients in remission after treatment for the first episode between the groups. The mean number of relapses per patient was similar between two groups. Further, the need for colectomy was similar between the groups. Thus, the treatment efficacy in both groups appeared to be similar. However, as seen in the first episode, the dose of steroids required for relapse was significantly smaller in the GMA group. Our results indicated that the early induction of GMA therapy significantly reduced steroid administration in the long-term clinical course of UC.

Hanai and colleagues specifically focused on steroid-dependent patients, and randomised 69 steroid-dependent UC patients to receive GMA therapy in addition to their standard drug therapy (n=46), or prednisolone 30 mg/day (n=23). At week 12, 83% of patients in the GMA group achieved remission, vs 65% in the steroid group, but statistical significance was not attained. The cumulative amount of prednisolone received was significantly lower in the GMA group than in the steroid group, although the rate of steroid-free patients was not significant. GMA appeared to be an effective adjunct to standard drug therapy of moderately severe UC by promoting remission and sparing steroids.

Figure 4 The cumulative proportion of patients without steroid-dependency.

Patients at risk

<table>
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</tbody>
</table>
Corticosteroid sparing effect of leucocytapheresis

Corticosteroid sparing effect of leucocytapheresis

can spare patients from corticosteroids, hospitalisation and surgery, it should be cost-effective.

Conflict of interest

None declared.

External funding

None.

References