Safety and Efficacy of Granulocyte and Monocyte Adsorption Apheresis in Patients With Active Ulcerative Colitis: A Multicenter Study

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Active ulcerative colitis (UC) is characterized by activation and infiltration of granulocytes and monocytes/macrophages into the colonic mucosa. The infiltrated leukocytes can cause mucosal damage by releasing degradative proteases, reactive oxygen derivatives, and proinflammatory cytokines. The aim of this trial (conducted in 14 specialist centers) was to assess safety and efficacy of granulocyte and monocyte adsorption apheresis in patients with active UC most of whom were refractory to conventional drug therapy. We used a new adsorptive type extracorporeal column (G-1 Adacolumn) filled with cellulose acetate beads (carriers) of 2 mm in diameter, which selectively adsorb granulocytes and monocytes/macrophages. Patients (n = 53) received five apheresis sessions, each of 60 minutes duration, flow rate 30 ml per minute for 5 consecutive weeks in combination with 24.4 ± 3.60 mg prednisolone (mean ± SE per patient per day, baseline dose). During 60 minutes apheresis, 26% of granulocytes, 19.5% of monocytes and 2% of lymphocytes adsorbed to the carriers. At week 7, 58.5% of patients had remission or improved, the dose of prednisolone was reduced to 14.2 ± 2.25 mg (n = 43). The apheresis treatment was fairly safe, only eight non-severe side effects (in 5 patients) were reported. Based on our results, we believe that in patients with active severe UC, patients who are refractory to conventional drugs, granulocyte and monocyte adsorption apheresis is a useful adjunct to conventional therapy. This procedure should have the potential to allow tapering the dose of corticosteroids, shorten the time to remission and delay relapse. J. Clin. Apheresis. 16:1–9, 2001.

Key words: diarrhea; prednisolone; granulocytes; monocytes/macrophages; inflammatory cytokines; LECAM-1; Adacolumn

INTRODUCTION

Ulcerative colitis (UC) is a recurrent inflammation of the colon and rectum that is characterized by rectal bleeding, diarrhea, fever, anorexia, and weight loss [1]. In active UC, there is activation and extravasation of large
numbers of granulocytes and monocytes/macrophages into the colonic mucosa [1,2]. The infiltrated leukocytes can cause extensive mucosal tissue injury by releasing degradative proteases [2–4], reactive oxygen derivatives [2,4–7], and proinflammatory cytokines [4,8,9]. It is believed that much of the watery diarrhea associated with UC is a result of injury to the absorptive epithelium, thus making these cells less capable of absorbing water. Further, there is evidence to suggest that the infiltration of leukocytes is mediated by the potent proinflammatory agents, TNF-α [9,10], leukotriene B4, and platelet-activating factor, as these three substances are elevated in inflamed mucosa [9,11,12].

The apparent association of granulocyte and monocyte/macrophage infiltration with mucosal injury has led to the view that these cells have an active role in UC [2–4] and that patients with UC may benefit from depletion of activated granulocytes and monocytes/macrophages by apheresis. Thus, several studies have indicated that leukocytapheresis is a useful adjunct to therapy after failure of conventional treatments [13–16]. A Japanese study of leukocytapheresis in the treatment of eight patients with UC and five with Crohn’s disease reported an 85% response rate [17]. In this study, we used the Adacolumn, which is a new adsorptive type granulocyte and monocyte apheresis device. The apheresis column is filled with cellulose acetate carriers which selectively adsorb granulocytes and monocytes/macrophages. The Adacolumn has already been used in the treatment of patients with rheumatoid arthritis and has shown promising safety and efficacy [18–20].

METHODS

Objective

The goal of this clinical trial was to assess safety and efficacy of the Adacolumn granulocyte and monocyte adsorption apheresis in patients with active ulcerative colitis (UC) most of whom were refractory to conventional drug therapy. This multicenter clinical investigation was conducted at 14 medical institutions throughout Japan in accordance with the GCP Guidelines for Medical Devices. The drug therapy was according to the guidelines set by the experts committee on inflammatory bowel disease, the Ministry of Health and Welfare of Japan, 1989. Owing to the nature of the treatment, an open-label study was conducted.

The Apheresis Column

The Adacolumn (G-1 column) is a new adsorptive type extracorporeal device. For this study, the unit was provided by JIMRO (351-1 Nishiyokote Machi, Takasaki, Japan). The Adacolumn has a capacity of about 335 ml, filled with 220 g cellulose acetate beads (about 35,000 pieces) of 2 mm in diameter (adsorptive carriers) bathed in sterile saline. The volume of circuit lines was 80 ml. For apheresis, a regular dialysis blood line (circuit lines), the Adacolumn and a pump were used.

Patient Selection and Disease Assessment

Of 60 recruited patients, 7 did not meet the inclusion criteria. The remaining 53 eligible patients were selected for Adacolumn apheresis treatment. The demographic of patients is shown in Table I. Patients included for this study satisfied the diagnostic criteria for ulcerative colitis (UC) set by the experts committee on inflammatory bowel disease, the Ministry of Health and Welfare of Japan, 1989. All included patients had active UC (total colitis, left-sided colitis, proctitis, or segmented colitis), which was confirmed by clinical symptoms, endoscopy (colonoscopic findings), histology, and contrast studies. Patients were sub-grouped according to moderate, severe, and fulminant UC. Patients with diarrhea six times or more per day, macroscopic bloody stool (+++), fever (37.5°C or higher), tachycardia (90 beats/minute or more), anemia (Haemoglobin, Hb 10 g/dL or less), erythrocyte sedimentation rate (ESR) of 30 mm or more were judged to have severe UC. The severity classification of UC was supported by endoscopic findings including, the mucous membrane bleeds easily at the point of touch accompanied by bloody mucus discharge; multiple erosions, ulcers, or pseudopolyposis. Patients with chronic
and persistent active UC while under medication were classified as having intractable UC.

Patients younger than 12 years or older than 76 years, pregnant or lactating women, patients with hypotension (systolic blood pressure 80 mmHg or lower), hypercoagulability, severe anemia (Hb 8 g/dL or less), or any other serious illness were excluded. The final form of the protocol was approved by the ethics committee of each institute. Further, the purpose of the study and the nature of the procedures involved were fully explained to each patient for obtaining written informed consent. If a patient was a minor, the consent of the patient and one of patient’s parents was obtained in writing.

Medications

Major drugs used in these patients were prednisolone (PSL, a common medication for UC), sulphasalazine (SAS), and 5-aminosalicylic acid (5-ASA). The medication was not changed during the 2 weeks prior to the start of the trial. The mean daily doses of PSL per patient at baseline and up to 2 weeks after the last apheresis are presented in Table II. There was no change in SAS or 5-ASA dosage during the trial period. At baseline, all patients were receiving PSL, but the amount of this steroid received by each patient varied and was based on the severity of UC. According to the study protocol, the dose of PSL could be reduced in line with UC disease improvement or remission. Drugs which were not known to directly affect the trial’s efficacy or adverse reaction were given when necessary. When surgery was to be performed during the trial, the patient’s participation in the trial was terminated at that time. There are three reasons for the decline in the number of patients in the subsequent weeks seen in Table II: a) remission of UC; b) it became necessary to treat the patient with medication, which was not indicated in the protocol (protocol violation); and c) patient decided to withdraw from the study.

Measurement of Leukocyte Adsorption

The number of leukocytes adsorbed to the carriers was calculated by subtracting the leucocyte count at the Adacolumn outflow from the count at the inflow multiplied by the apheresis time [19,20]. Differential blood cell counting was done with a THMS H-1 (Technicon). As a general rule, adsorbed cell count was measured during the first Adacolumn apheresis treatment. Blood cell counts were measured immediately prior to start of apheresis (inflow), 15, 30 and 60 min after the start of apheresis. The values for the column inflow at time 0 were taken as the pre-apheresis blood cell counts; the counts at the column outflow were taken as the post-column counts. The difference between column inflow and column outflow was taken as the fraction of blood components adsorbed to the Adacolumn carriers.

Assessment of UC Severity

At baseline, just before third apheresis and at the end of week 7, the following items were investigated for...
assessing efficacy or UC progress (− = absent; ± = mild; + = moderate; and ++ = severe): 1) blood in the stool (present/absent); 2) diarrhea; 3) abdominal pain (−, ±, +, and ++); 4) fecal characteristic (watery, mud-like, soft, moderately firm, firm); 5) bloated feeling in the abdomen (−, ±, +, ++); 6) anal pain (−, ±, +, ++); 7) loss of appetite (−, ±, +, ++); 8) malaise (−, ±, +, ++); 9) morning body temperature; 10) body weight; 11) multiple erosions, ulcers or polyposis in the mucosal membrane; 12) mucosal membrane bleeding at the point of contact; 13) presence or absence of mucosal vascular patterns; 14) inflammatory markers, ESR and CRP (C-reactive protein).

Assessment of Efficacy

Currently, there is no single method which has been widely used for measuring UC disease activity in clinical studies [21]. In this study, the overall improvement of UC disease was evaluated by combining three categories of data: clinical findings (including stool frequency, absence or presence of blood in the stool, abdominal pain, and body temperature), endoscopic findings (including biopsy results), and inflammation markers. These three categories of results were used to determine responders. If a patient was withdrawn from the study for the reasons given in the section on medication above, then the efficacy in that patient was assessed at that time.

Statistical Analysis

Where appropriate, the results are presented as mean ± SE. Changes before and after treatment were analyzed by Wilcoxon signed rank test. The level of significance was set at 5%; the SAS (Statistical Analysis System, SAS Institute Japan, Ltd.) carried out all the statistical analyses.

RESULTS

Changes in CRP, ESR, Hb, and Platelets

CRP and ESR are known as inflammation markers. The plasma levels of CRP (mg/dL) were 1.84 ± 0.3 (n = 53) and 0.95 ± 0.1 (n = 50) for baseline and end of the treatment, respectively (P = 0.019). Similarly, ESR (mm/hour) values were 24.55 ± 2.9 (n = 49) and 16.72 ± 2.6 (n = 46) for baseline and end of the treatment, respectively (P = 0.004). Therefore, consistent with improvement of UC, CRP, and ESR were both significantly lower at the end of the treatment. Hb (g/dL) values were 11.1 ± 0.32 (n = 53) and 11.5 ± 0.3 (n = 51) for baseline and end of the treatment, respectively, showing no marked change in Hb during this study. Platelet counts (10^3/μL) were 328 ±16 (n = 53) and 292 ±12 (n = 51) for baseline and end of the treatment, respectively (P = 0.003). The results show a significant fall in platelet counts during the treatments. The (n) values indicate the number of patients from whom samples were available.

Changes in CRP, ESR, Hb, and Platelets

### Table III. Total Leukocyte Counts at Adacolumn Inflow and Outflow (first apheresis treatment) for 53 Patients With Ulcerative Colitis Who Received Adacolumn Apheresis*

<table>
<thead>
<tr>
<th>Leukocyte population</th>
<th>Inflow</th>
<th>Outflow</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes (×10^9)</td>
<td>9.5 ± 0.64</td>
<td>7.0 ± 0.491</td>
<td>0.001</td>
</tr>
<tr>
<td>Monocytes (×10^9)</td>
<td>0.46 ± 0.04</td>
<td>0.37 ± 0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphocytes (×10^9)</td>
<td>2.11 ± 0.14</td>
<td>2.07 ± 0.13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Peripheral blood granulocyte numbers (X 10^3/μL)</td>
<td>6.408 ± 0.4328</td>
<td>5.010 ± 0.4126</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Total count was measured by using the blood leukocyte count, flow rate and apheresis time. The number of peripheral blood granulocytes at baseline and at week 7 (see text and the legend to Table II for further details). Mean ± SE values are shown.

Changes in the Dose of Prednisolone

The mean daily doses of PSL per patient at baseline and up to 2 weeks after the last apheresis are presented in Table II. PSL dose could be reduced in line with improvement of UC disease activity or remission. Therefore, as shown in Table II, the average dose of PSL during the apheresis treatment was reduced from week 3 to about 58% of the baseline level.

Adsorption of Leukocytes to the Adacolumn Carriers

Table III shows the total numbers of granulocytes, monocytes and lymphocytes which entered and left the Adacolumn during 60 minutes apheresis. As shown, there was a significant fall in granulocyte and monocyte counts, but the lymphocyte count did not fall significantly at the column outflow, indicating that the Adacolumn carriers selectively adsorb granulocytes and monocytes. Up to 90% of retained leukocytes were granulocytes. Table III also shows that during the study, the average number of granulocytes in the patients’ peripheral blood decreased significantly. Further, as reported below, in addition to a reduction in the number of granulocytes and monocytes, peripheral blood leukocytes (PBL) were downregulated by apheresis, less cytokine production and L-selectin expression. It should be noted that the UC patients included in this study had raised granulocyte counts, about two times the normal value, 6.6 × 10^3/μL compared with 3.4 × 10^3/μL for normals [22].

Apheresis Induced Suppression of Cytokine Production

Cytokine production by leukocytes was measured using a previously described method [10]. Figure 1 shows production of proinflammatory cytokines [4,23–25], TNF-α, interleukin -1β (IL-1β), IL-6, and IL-8 by lipopolysaccharide (LPS) stimulated whole blood leukocytes of patients with UC, taken at the Adacolumn inflow and outflow points. As shown, apheresis significantly sup-
pressed production of these cytokines and since the inflow blood represents peripheral blood, the results indicate that Adacolumn apheresis is associated with immunomodulation (less proinflammatory cytokines).

Apheresis Induced Changes in Leukocyte Adhesion Molecules

To infiltrate tissues, granulocytes must first adhere to endothelial cells and then be able to transmigrate into tissues. Leukocyte rolling, which is followed by adhesion, is mediated by LECAM-1 (leukocyte-endothelial cell adhesion molecule-1, L-selectin) expressed on leukocytes [8,24–26]. The leukocyte integrin, Mac-1 (CD11b/CD18) is expressed predominantly on monocytes/macrophages and granulocytes, to a higher extent when these cells are activated [4,8,24,25]. By using a published method [26], the expression of LECAM-1 and Mac-1 on leukocytes in the blood at the Adacolumn inflow and outflow was investigated with flow cytometry. Figure 2 shows that in patients with UC, after apheresis, expression of LECAM-1 on the unadsorbed leukocytes was downregulated. In contrast, expression of Mac-1 was upregulated. On the basis of the aforementioned, downregulation of LECAM-1 by the apheresis column can...
result in impaired leukocyte-endothelial cell interactions, leukocyte trafficking, and while LECAM-1 is downregulated, upregulation of Mac-1 is not sufficient to promote leukocyte trafficking because the initial step in leukocyte-endothelial cell interaction (rolling) is downregulated. The expression of adhesion molecules was determined as percentage of LECAM-1 (or Mac-1) positive cells × MFI (mean fluorescence intensity) in a randomly selected 21 patients with ulcerative colitis who received Adacolumn apheresis therapy.

**Efficacy of Treatments**

Assessment of efficacy was based on the criteria described above (Methods). Table 4 shows the average number of stools per day during the study. Stool number was significantly reduced by the apheresis treatment ($P=0.0001$, at the end of therapy). Table IV also shows that the number of patients with bloody stool decreased dramatically during the apheresis therapy. Complete remission was achieved in 11 of 31 patients who responded to the apheresis therapy. Figure 3 shows an endoscopic photograph of the sigmoid colon from a patient with severe and steroid-resistant UC. Section (a) taken at baseline shows deep and extensive mucosal ulcers. Section (b) taken from the same site after five apheresis sessions (week 7) shows revascularisation of the mucosa.

**Treatment Safety**

A total of eight non-severe adverse reactions in five patients were reported during the study period. These were one dizziness, one dizziness on standing, one nausea, one duodenal perforation, two incidences of fever, and two incidences of flushing. However, no patient discontinued the treatment due to adverse reaction, but three of five patients received medical treatment.

**Discussion**

Patients with autoimmune disease are known to have raised peripheral blood granulocytes [4,8,22], which can be activated by immune complexes [27] and soluble factors [4,8,11,12]. The activated leukocytes can produce inflammatory cytokines and promote inflammation. In line with these assertions, granulocyte counts in our UC patients were almost double the level in healthy controls [22]. Further, it has been shown that inflammatory mediators inhibit apoptosis and prolong neutrophil functional longevity [28]. Based on this understanding, we thought that selective granulocyte and monocyte apheresis should be a logical approach to reduce the number and suppress the activity of granulocytes in patients with UC. We also think that the Adacolumn cellulose acetate carriers may enhance apoptosis of activated granulocytes. Thus, when granulocytes from normal donors were first activated by a small dose of LPS and then were exposed to the cellulose acetate carriers, apoptosis was significantly enhanced (Kashiwagi and Shimoyama, manuscript in preparation).

Currently, the use of steroid-based drugs is a common strategy for treating UC. However, since large doses of steroids are often necessary to control active UC and the treatment may need to be continued over a long period of time, the drugs become less effective with time (the disease becomes resistant to drugs). Finally the drug therapy may have to be stopped due to severe side effects and some patients may opt for surgery [29]. Since granulocytes and monocytes are understood to contribute to the tissue injury seen in UC, depletion of these cells by apheresis could be a useful adjunct to therapy after failure of conventional treatments. Alternatively, based on the results of the present clinical trial, granulocyte and monocyte apheresis could be a useful adjunct to therapy after failure of conventional treatments.

**TABLE IV. Average Stool Frequency (times/day) at Baseline and During Adacolumn Apheresis Treatment**

<table>
<thead>
<tr>
<th>Time point</th>
<th>Stool frequency</th>
<th>Presence of blood in the stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>53.0</td>
<td>Yes (n) 45, No (n) 8</td>
</tr>
<tr>
<td>Week 2</td>
<td>52.0</td>
<td>Yes (n) 37, No (n) 15</td>
</tr>
<tr>
<td>Week 3</td>
<td>50.0</td>
<td>Yes (n) 29, No (n) 21</td>
</tr>
<tr>
<td>Week 4</td>
<td>42.0</td>
<td>Yes (n) 21, No (n) 24</td>
</tr>
<tr>
<td>Week 5</td>
<td>39.0</td>
<td>Yes (n) 15, No (n) 24</td>
</tr>
<tr>
<td>Week 7</td>
<td>38.0</td>
<td>Yes (n) 12, No (n) 26</td>
</tr>
</tbody>
</table>

*Patients (n) received one apheresis per week during weeks 1 to 5; weeks 6 and 7 represent the follow up period. Further details as in the legend to table 2 (n = number of patients).
monocyte adsorption apheresis could be used to lower the dose of steroids and thus minimize treatment side effects. Based on a similar understanding, the Adacolumn was used to treat patients with rheumatoid arthritis [18–20,22].

In this study as well as in rheumatoid arthritis studies [19], production of proinflammatory cytokines, TNF-α, IL-6 and IL-1β by PBL was markedly suppressed by Adacolumn apheresis. This was unexpected because during 1 hour apheresis, only 1.8 liters of patient’s blood are exposed to the Adacolumn carriers. TNF-α is reported to be a major pathologic factor in inflammatory bowel disease [29]. For example, it is a strong stimulator of the leukocyte chemoattactant/activator protein, IL-8 release.

Table V. Efficacy of Adacolumn Apheresis Treatment With Respect to Various Factors (at baseline) in Sub Groups of Patients With Ulcerative Colitis (UC)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>31 responder 22 non-responder 58.5</td>
</tr>
<tr>
<td>First attack of UC</td>
<td>8 responder 3 non-responder 72.7</td>
</tr>
<tr>
<td>Relapse of UC</td>
<td>23 responder 19 non-responder 54.8</td>
</tr>
<tr>
<td>Severe UC</td>
<td>10 responder 9 non-responder 52.6</td>
</tr>
<tr>
<td>Moderate UC</td>
<td>21 responder 13 non-responder 61.8</td>
</tr>
<tr>
<td>Non-intractable UC</td>
<td>10 responder 6 non-responder 62.5</td>
</tr>
<tr>
<td>Intractable UC</td>
<td>15 responder 14 non-responder 51.7</td>
</tr>
<tr>
<td>Duration of UC (year)</td>
<td>9 responder 6 non-responder 60.0</td>
</tr>
<tr>
<td>Cumulative dose (mg) of prednisolone from the start of UC</td>
<td>9 responder 4 non-responder 69.2</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>15 responder 10 non-responder 60.0</td>
</tr>
</tbody>
</table>
| Complete remission was achieved in 11 of the 31 responders to apheresis treatment (based on assessments at week 7).
Cellulose acetate is an efficient activator of the complement which these cells phagocytose opsonized particles [30]. L-selectin which has a key initiating role in leukocyte trafficking from blood into tissues [8,24–26] was downregulated following apheresis. This action could impair leukocyte infiltration into the mucosal tissue. On the basis of these observations, the improvements achieved in UC disease following Adacolumn apheresis may not be fully attributed to removal of a fraction of granulocytes and monocytes; it might be partly attributed to immunomodulation via suppression of inflammatory cytokines and leukocyte trafficking.

Regarding depletion of granulocytes in the peripheral blood by apheresis, it can be argued that in practice this may be impossible to achieve because the elimination of circulating leukocytes may quickly be followed by reticuloendothelial system response to replace the lost leukocytes. Additionally, it may need to be ascertained that the depletion of circulating granulocytes is paralleled by a reduction in the mucosal level of these cells. However, as indicated above, the patients recruited for this study had raised granulocyte counts and all had active UC at entry and apheresis resulted in a significant decrease in the number of these cells at the column outflow as well as in the peripheral blood. Further, endoscopy together with biopsy revealed lack of extensive leukocyte infiltration; instead a marked mucosal revascularization was seen in patients who responded to the apheresis therapy. The reduced ability of leukocytes to produce inflammatory cytokines could also have contributed to suppression of leukocyte infiltration.

When a patient is presented with active UC, it is a common strategy to administer steroids like PSL or increase the existing dose; the drug dose is then reduced or stopped when the disease improves or remission is achieved. In line with this practice, by introducing granulocyte and monocyte adsorption apheresis in this study, we could reduce the average dose of PSL in line with improvement of UC severity and remission. Additionally, when patients were sub-grouped based on disease factors, the response to Adacolumn apheresis was better in patients with severe UC, long duration of UC, and long period of steroid therapy. These observations may suggest that granulocytes are strongly associated with the UC disease in these conditions.

The data provided by this study and those provided by studies in patients with RA [18–20,22] show that the Adacolumn carriers selectively adsorb granulocytes and monocytes, without significantly adsorbing lymphocytes. This may be explained as follows. Granulocytes (neutrophils), monocytes/macrophages are phagocytic cells and the mechanism by which the cellulose acetate carriers retain granulocytes, monocytes/macrophages, but not lymphocytes is most likely to be similar to the process by which these cells phagocytose opsonized particles [30]. Cellulose acetate is an efficient activator of the complement cascade, consequently, soon after contact with human blood, it becomes coated with complement fragments like C5a. Each point on the beads then resembles an opsonized particle and therefore, a site of attraction for the phagocytic cells. Furthermore, patients with autoimmune disease are known to have immune complexes in their plasma [27] that are adsorbed to cellulose acetate and together with C5a, mediate granulocyte and monocyte arrest via the Fc receptor (CD16).

Conclusions

It is widely believed that granulocytes and monocytes contribute to tissue injury seen in UC. The principal aim of this study was to assess the safety and efficacy of selective granulocyte and monocyte apheresis in patients with active UC most of whom were resistant to conventional drug treatment. The apheresis therapy together with low doses of prednisolone were associated with reduced UC severity and remission. The apheresis was well tolerated; only a small number of non-severe side effects were reported. The results suggest that in patients with active and steroid-resistant UC, granulocyte and monocyte adsorption apheresis could be a useful adjunct to therapy after failure of conventional treatments.

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