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EDITORIAL

Steroid-sparing strategies in the management of ulcerative colitis: Efficacy of leukocytapheresis

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Abstract

Active ulcerative colitis (UC) is frequently associated with infiltration of a large number of leukocytes into the bowel mucosa. Leukocytapheresis is a novel nonpharmacologic approach for active UC, in which leukocytes are mechanically removed from the circulatory system. Current data indicate that leukocytapheresis is efficacious in improving response and remission rates with excellent tolerability and safety in patients with UC. Corticosteroid therapy remains a mainstay in the treatment of active UC; however, long-term, high doses of corticosteroids usually produce predictable and potentially serious side effects. If leukocytapheresis can spare patients from exposure to corticosteroids, the risk of steroid-induced adverse events should be minimized. This may be of great benefit to patients because severe side effects of steroids seriously impair health-related quality of life. In this article, we reviewed current evidence on whether leukocytapheresis can avoid or reduce the use of corticosteroids in the management of patients with UC. Several studies have shown that leukocytapheresis was effective for steroid-naïve patients with active UC. Furthermore, both short-term and long-term studies have demonstrated the steroid-sparing effects of leukocytapheresis therapy in patients with UC. Although the evidence level is not striking, the available data suggest that leukocytapheresis can avoid or reduce the use of corticosteroids in the management of UC. Large, well-designed clinical trials are necessary to more accurately evaluate the steroid-sparing effects of leukocytapheresis in the management of UC.

Key words: Corticosteroid; Granulocyte and monocyte adsorptive apheresis; Leukocytapheresis; Steroid-naïve patients; Steroid-sparing effect; Ulcerative colitis

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INTRODUCTION

Active ulcerative colitis (UC) is frequently associated with infiltration of a large number of leukocytes into the bowel mucosa[1]. The infiltrated leukocytes release degradative enzymes, oxygen derivatives and proinflammatory substances that can cause bowel injury and promote further inflammation[2,3]. Removing excess and activated circulating leukocytes by apheresis has the potential to improve the condition of patients with inflamed bowels.

LEUKOCYTAPHERESIS

Leukocytapheresis is a novel nonpharmacologic approach

for active UC, in which leukocytes are mechanically removed from the circulatory system[4-7]. Different apheresis techniques remove different types of leukocytes, and have different adsorption capacities. The two most common techniques involve drawing blood *via* a venous catheter, pumping it through a column containing cellulose acetate beads (Adacolumn) or a filter of nonwoven polyester fibers (Cellsorba), thereafter returning it to the circulatory system. As blood passes through the system, leukocytes adhere to the beads or filter. Leukocytapheresis appears to avoid and control an excess of cytokines by removing activated leukocytes from patient peripheral blood and inflamed bowels[5,7]. However, the detailed biochemical mechanisms underlying the effects of leukocytapheresis remain largely unknown.

CORTICOSTEROIDS

Corticosteroid therapy remains a mainstay in the treatment of active UC[8-11]. Patients frequently experience improvement in their symptoms within days of starting corticosteroids. During an acute severe exacerbation, approximately two-thirds of patients will respond to intravenous corticosteroid therapy. For steroid-refractory patients, options are limited to surgery or second-line agents, such as cyclosporine or infliximab, used in an attempt to avoid colectomy.

In the study by Faubion *et al*[12], 63 patients with active UC were treated with corticosteroids. Short-term outcomes (30 d) were complete remission in 54% of patients, partial remission in 30%, and no response in 16%. One-year outcomes were prolonged response in 49% of patients, corticosteroid dependence in 22%, and operation in 29%. This study underlines the fact that most patients with UC initially respond to steroids, but after one year a significant proportion loses the response; this leads to steroid-dependency or the need for surgery, even among those who initially responded to the treatment. The pathophysiology of corticosteroid resistance and dependency in UC is poorly understood[13]. Leukocytapheresis removes from the body blood cells that contribute to UC and, therefore, unlike corticosteroids, it is not expected to induce dependency or refractoriness.

EFFICACY AND SAFETY OF LEUKOCYTAPHERESIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICAL TRIALS

The data obtained from uncontrolled studies[14-18] are generally quite consistent: a high response rate has been achieved in corticosteroid-naïve patients and a remission rate of approximately 50% has been achieved in patients with steroid-dependent or steroid-refractory UC. Additionally, leukocytapheresis is safe and well tolerated[14-18]. The largest randomized, double-blind, sham-controlled study of Adacolumn leukocytapheresis therapy failed to demonstrate efficacy for the induction of clinical remission or response in patients with moderate-to-severe UC[19]. A number of meta-analyses[20-22] were conducted to assess the safety and efficacy of leukocytapheresis compared with conventional pharmacotherapy in patients with UC. In the trials that compared leukocytapheresis and corticosteroids, side effects were much less frequent in patients treated with leukocytapheresis. Few severe adverse events were observed during leukocytapheresis therapy. Unlike corticosteroids, leukocytapheresis is associated with an excellent safety and tolerability profile. Furthermore, leukocytapheresis induces a clinical remission in a higher proportion of UC patients as compared to conventional medical therapy. However, many of the studies evaluated in the meta-analyses were conducted in Japanese patients, which may limit generalizability. High-quality randomized controlled trials (RCTs) comparing leukocytapheresis with conventional medical treatment or sham procedure in Western populations are required[20-22].

POTENTIAL ADVANTAGES OF LEUKOCYTAPHERESIS OVER CORTICOSTEROIDS

Long-term, high doses of corticosteroids usually produce predictable and potentially serious side effects. If leukocytapheresis can spare patients from exposure to corticosteroids, the risk of steroid-induced adverse events should be minimized. This may be of great benefit to patients because severe side effects of steroids seriously impair health-related quality of life. In this article, we reviewed current evidence on whether leukocytapheresis can avoid or reduce the use of corticosteroids in the management of patients with UC.

FACTORS AFFECTING EFFICACY OF LEUKOCYTAPHERESIS

In a number of studies[23,24], factors affecting the efficacy of leukocytapheresis were identified. We conducted a prospective study to identify factors affecting clinical and endoscopic efficacies of Adacolumn leukocytapheresis in patients with active UC[23]. In the multivariate analysis, the dose of prednisolone administered at entry and the cumulative dose of prednisolone administered before entry were significant independent factors for both clinical and endoscopic remission, and negatively impacted the efficacy of leukocytapheresis. It appears that steroid-naïve patients and patients on low dose steroid and short duration of exposure respond to leukocytapheresis. Suzuki *et al*[24], searched for predictors of clinical response to Adacolumn leukocytapheresis. First UC episode and short disease duration appeared to be good predictors of response to leukocytapheresis. From these data, leukocytapheresis may be a promising candidate therapy for steroid-naïve patients with active UC. Furthermore, leukocytapheresis can be an effective first-line treatment in

Table 1 Leukocytapheresis for steroid-naïve patients with active ulcerative colitis

Ref.	Patients (*n*)	Leukocytapheresis (sessions/wk)	Remission[1] rate (%)
Hanai *et al*[14]	Steroid-naïve 8 (steroid-refractory 31)	Adacolumn 11/11	Naïve 88 (refractory 81)
Suzuki *et al*[15]	20	Adacolumn 5-10/2.5-5	85
Tanaka *et al*[25]	Steroid-naïve 26 (steroid-dependent 19)	Adacolumn 11 /12	Naïve 85 (dependent 58)
Nishioka *et al*[26]	9	Cellsorba 10 /10	33 (89 improved)
Umehara *et al*[27]	18	Cellsorba 5 /5	61

[1]Remission was defined as a clinical activity index (CAI) decrease to 4 or less and mucosal vascular patterns became at least partly visible in the studies by Hanai *et al*[14], Suzuki *et al*[24], and Nishioka *et al*[26], a CAI decrease to 4 or less in the study by Tanaka *et al*[25], and a CAI decrease to less than 4 in the study by Umehara *et al*[27].

patients with active UC.

LEUKOCYTAPHERESIS FOR STEROID-NAÏVE UC

Leukocytapheresis has been mainly used for patients with steroid-dependent or steroid-refractory moderate-to-severe UC. About half of patients with steroid-dependent or steroid-refractory UC achieve clinical remission during a course of leukocytapheresis therapy[20-22]. So far, five small-scale observational studies[14,15,25-27] have evaluated the efficacy and safety of leukocytapheresis for steroid-naïve patients with active UC. Of these five studies, one study[14] also included steroid-refractory patients, and one study[25] steroid-dependent patients. Another study[26] compared the outcomes of steroid-naïve patients treated with leukocytapheresis and corticosteroid therapy.

A brief summary of the five studies is presented in Table 1. In the short-term, the majority of patients achieved clinical improvement. The remission rate immediately after leukocytapheresis therapy ranged from 33% to 88%[14,15,25-27]. Quantitative pooling of data was not feasible due to the diversity of interventions and outcome measures among the studies. In a prospective study by Hanai *et al*[14], 81% of steroid-refractory and 88% of steroid-naïve patients achieved clinical remission one week after the last apheresis session. At 12 mo, 79% of patients had maintained their remission. In a prospective study by Suzuki *et al*[15], 85% of patients achieved clinical remission during a course of leukocytapheresis therapy. At eight months, 60% of patients had maintained their remission. In the study by Tanaka *et al*[25], the response rate was 85% in steroid-naïve patients and 58% in steroid-dependent patients. On average, remission was sustained with 5-aminosalicylic acid (5-ASA) for 7.8 mo in the responders. This is the first report showing a striking difference in clinical response to Adacolumn leukocytapheresis between steroid-naïve and steroid-dependent patients. In a controlled study by Nishioka *et al*[26], 29 steroid-naïve patients were selected to be treated with Cellsorba leukocytapheresis ($n = 9$) or steroids ($n = 20$). In the steroid group, patients with moderately active disease received 0.5 mg/kg/d of prednisolone and those with severe disease 1.0 mg/kg/d. Eight patients (89%) in the apheresis group and 16 (80%) in the steroid group showed clinical improvement, and three (33%) in the apheresis group and seven (35%) in the steroid group achieved clinical remission. Three major adverse effects were observed in the steroid group, but none were observed in the apheresis group. The efficacy and safety of leukocytapheresis were equivalent, and in terms of severe adverse effects, superior to those of steroid therapy. In the study by Umehara *et al*[27], 18 steroid-naïve patients with moderately active UC received weekly leukocytapheresis therapy with Cellsorba for five consecutive week. The remission rates at 8 and 48 wk after the last apheresis session were 61% and 28%, respectively. At 48 wk after achieving remission, the relapse rate was 55%, and the duration to relapse was 8.7 mo. In all studies[14,15,25-27], leukocytapheresis was well tolerated, and no severe side effects were observed.

EFFICACY OF LEUKOCYTAPHERESIS WITHOUT CONCOMITANT STEROID THERAPY

In patients with moderately to severely active UC who failed to respond to optimal doses of 5-ASA compounds, systemic corticosteroids should be used. A few studies[17,28] evaluated the efficacy and safety of leukocytapheresis without concomitant steroid therapy for patients who failed to respond to 5-ASA compounds. In our prospective study[17], 30 consecutive patients with active distal UC were treated with weekly Adacolumn leukocytapheresis (a total of five sessions). During treatment, corticosteroid was not given. The median disease activity index score significantly decreased from six to two. Clinical remission was achieved in 21 patients (70%) after the last apheresis session. No serious side effects were observed. Ashida *et al*[28] conducted a multicenter study to investigate the efficacy of leukocytapheresis without concomitant steroid therapy in patients with active UC. Twenty patients were treated with Cellsorba leukocytapheresis (twice a week for three weeks). The Lichtiger's clinical activity index score significantly decreased from 11.7 to 6.6 after the treatment. Of the 20 patients, 15 (75%) responded, and 7 (35%) achieved complete remission. No serious adverse reactions were observed.

In an RCT by Bresci *et al*[29], 80 patients with active UC were randomly divided into two treatment groups: patients in the apheresis group received a five-session (one session per week) treatment with Adacolumn leukocytapheresis, and those in the steroid group were treated with methylprednisolone. Concomitant therapy with oral

5-ASA (2.4 g/d) was maintained in both groups. Patients who achieved remission were clinically and endoscopically followed for 12 mo after the end of leukocytapheresis or methylprednisolone therapy. Remission was achieved in 73% of patients in the apheresis group *vs* 50% in the steroid group. Leukocytapheresis was superior to methylprednisolone for the treatment of active UC, even though no statistically significant difference was observed. After a 12-mo follow up, a sustained remission was recorded in 40% of patients in the apheresis group *vs* 25% in the steroid group. Patients who had obtained remission after a course of leukocytapheresis showed fewer relapses during the follow up compared to those treated with methylprednisolone. During leukocytapheresis, only a transient mild headache was recorded in 10% of patients, whereas side effects were observed in 50% of those treated with methylprednisolone. The incidence of side effects in the apheresis group was significantly lower than that in the steroid group. Leukocytapheresis therapy seems able to maintain the condition of remission for a longer time after a flare.

STEROID-SPARING EFFECTS OF LEUKOCYTAPHERESIS

Leukocytapheresis could be an alternative treatment for steroid-dependent UC. A number of clinical trials[30-34] evaluated the steroid-sparing effects of leukocytapheresis in patients with UC. Quantitative pooling of data was not feasible due to the diversity of interventions and outcome measures among the studies.

In an RCT by Hanai *et al*[30], 69 patients with steroid-dependent UC were assigned to receive Adacolumn leukocytapheresis in addition to standard drug therapy (apheresis group, $n = 46$) or prednisolone (steroid group, $n = 23$). At week 12, 83% of patients in the apheresis group achieved remission *vs* 65% in the steroid group. During the 12 wk of treatment, the cumulative amount of prednisolone received per patient was significantly lower in the apheresis group than in the steroid group (1157 mg *vs* 1938 mg). Adacolumn leukocytapheresis therapy appeared to be an effective adjunct to standard drug therapy of moderately severe UC by promoting remission and sparing steroids.

The therapeutic benefit of leukocytapheresis in the maintenance of remission was additionally elucidated in a randomized pilot trial by Emmrich *et al*[31]. Twenty patients with chronic active UC were treated weekly with Cellsorba leukocytapheresis for five weeks. A significant decrease in the activity index was observed. Fourteen patients achieved clinical remission, and mucosal healing was observed endoscopically in six patients. After randomization these 14 patients in remission entered a second period of either monthly leukocytapheresis ($n = 8$) or no further treatment ($n = 6$). In both groups, steroids were tapered down. After six months, five patients (63%) in the apheresis group remained in remission *vs* one patient (17%) in the control group. These results suggest leukocytapheresis offers a therapeutic option in the induction and the maintenance of remission in chronic active UC.

In a prospective study by Cabriada *et al*[32], 18 patients with steroid-dependent UC were treated with leukocytapheresis plus steroids after failure or intolerance to immunomodulators. Clinical and endoscopic examinations were conducted at one month after the last apheresis session and at 12 mo. The clinical, endoscopic remission and the relapse during the one-year follow-up were evaluated. Clinical remission was achieved in 10 patients (55%) after the treatment. At one year, sustained steroid-free clinical remission was observed in nine patients (50%). A tendency for sustained remission at one year was observed when initial endoscopic remission was achieved. These results suggest that initial remission can be maintained at one year in half of the patients without the need for additional steroids. Complete remission and endoscopic mucosal healing is proposed as an objective for achieving a lasting response.

Cabriada *et al*[33] conducted a cohort study using a nationwide database in order to investigate short-term and long-term efficacies of leukocytapheresis for the management of steroid-dependent UC. One hundred and forty-two patients with steroid-dependent UC were treated with Adacolumn leukocytapheresis therapy. At one month after the last scheduled apheresis session, 68% of patients achieved clinical response, including 37% with steroid-free clinical remission. In the long-term, at six and 12 mo, 41% and 36% of patients were in clinical remission, respectively. Although this large-scale observational trial is uncontrolled, it clearly shows that Adacolumn leukocytapheresis allows long-term steroid-free clinical remission in up to one third of steroid-dependent UC patients.

Our recent study[34] was conducted to determine if the introduction of Adacolumn leukocytapheresis at an early stage reduces corticosteroid administration and steroid dependency in the long-term. Twenty patients were treated with Adacolumn leukocytapheresis, with or without corticosteroids (apheresis group), and 20 patients were given corticosteroids without leukocytapheresis (steroid group). During a five-year follow-up period, five patients in the apheresis group did not require corticosteroids. The mean dose of steroid administered during the five years was significantly lower in the apheresis group than in the steroid group (2141 mg *vs* 5443 mg). Furthermore, the incidence of steroid-dependence was significantly lower in the apheresis group at the end of the study (5% *vs* 35%). In patients with first UC episode, Adacolumn leukocytapheresis therapy at an early stage significantly reduces steroid administration and steroid-dependency in the long-term.

TREATMENT COST OF LEUKOCYTAPHERESIS

When selecting a treatment option, the cost must be an

important factor. The cost of leukocytapheresis therapy (approximately $ 1700 for one session with Adacolumn) is much higher as compared with corticosteroids. However, if leukocytapheresis can spare patients from corticosteroids, and reduce the incidence of steroid-dependency, hospitalization and surgery, it should be cost-effective.

CONCLUSION

Although the evidence level is not striking, the available data suggest that leukocytapheresis can avoid or reduce the use of corticosteroids in the management of UC. Large, well-designed clinical trials are necessary to more accurately evaluate the steroid-sparing effects of leukocytapheresis in the management of UC.

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