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Alimentary Tract

Efficacy and safety of granulocyte and monocyte adsorption apheresis for ulcerative colitis: A meta-analysis

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ABSTRACT

Background: Safe and effective treatments are required for patients with ulcerative colitis. It was suggested that granulocyte and monocyte adsorption apheresis might play an important role for ulcerative colitis. Therefore, a meta-analysis was performed.
Methods: Medline and the Cochrane controlled trials register were used to identify randomized controlled trials comparing granulocyte and monocyte adsorption apheresis with corticosteroids, and comparing intensive with conventional apheresis in patients with ulcerative colitis.
Results: Nine randomized trials were eligible for inclusion criteria. According to pooled data, granulocyte and monocyte adsorption apheresis is effective for inducing clinical remission in patients with ulcerative colitis compared with corticosteroids (odds ratio, 2.23; 95% confidence interval: 1.38–3.60). However, the efficacy of granulocyte and monocyte adsorption apheresis was not dependent on the number of apheresis sessions. The intensive apheresis (≥2 sessions per week) is more effective for inducing clinical remission than weekly apheresis (odds ratio, 2.10; 95% confidence interval: 1.12–3.93). The rate of adverse events by apheresis was significantly lower than that by corticosteroids (odds ratio, 0.24; 95% confidence interval: 0.15–0.37).
Conclusion: Our meta-analysis reveals that intensive granulocyte and monocyte adsorption apheresis is a safe and effective treatment with higher rates of clinical remission and response for ulcerative colitis compared with corticosteroids.

1. Introduction

Ulcerative colitis (UC) is a chronic relapsing gastrointestinal disorder characterized by inflammation of the colonic mucosa [1]. 5-Aminosalicylates (5-ASA) and corticosteroids are conventionally used as treatment for UC. 5-ASA, such as mesalazine, is used as initial induction and maintenance therapy for clinical remission in UC patients [2–4]. In patients with UC refractory to 5-ASA, administration of corticosteroids is considered the next main strategy for induction therapy [5,6]. Recent evidence indicates that calcineurin inhibitors and anti-tumour necrosis factor (TNF)-α agents are effective treatments for patients with UC refractory to corticosteroids [7–10]. These immunosuppressive therapies, however, are associated with several adverse events, such as opportunistic infection, infusion reaction and bone marrow suppression [11,12]. Moreover, recent reports suggest that the combination therapy with immunomodulators and anti TNF-α agents might be associated with an increased risk of malignancy, such as malignant lymphoma [13,14]. Therefore, less hazardous and safer long-term treatments are needed for maintenance of clinical remission in patients with UC.

The pathophysiology of UC remains unclear. UC is associated with an increase in circulating leukocytes and immune complexes [15,16]. Neutrophil granulocytes and monocytes/macrophages produce proinflammatory cytokines such as TNF-α and interferon (IFN)-γ, and these proinflammatory cytokines contribute to intestinal inflammation in UC [17,18]. The level of faecal calprotectin, a member of the Ca^{2+}-binding S100 family of proteins that is expressed in the cytoplasm of activated neutrophils and has proinflammatory properties, is related to the severity of UC [19], suggesting that removal of circulating neutrophil granulocytes is a theoretically rational treatment for UC.

Granulocyte and monocyte adsorption apheresis (GMAA) using Adacolumn® (JIMRO, Takasaki, Gunma, Japan) to remove activated neutrophil granulocytes is thus a promising therapeutic option for patients with UC [20,21]. The column is filled with cellulose acetate

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beads (leucocyte apheresis carriers) of 2 mm in diameter that are bathed in sterile saline. These leucocyte apheresis carriers selectively adsorb granulocytes and monocytes/macrophages that bear Fcγ and complement receptors. Several clinical trials have reported the efficacy of GMAA for the treatment of UC [22,23]. Moreover, intensive apheresis with more than two sessions per week induces rapid clinical remission in patients with active UC compared with weekly GMAA (one session per week) [24]. It remains unclear, however, whether GMAA is not inferior to corticosteroids for inducing the remission of UC because numerous clinical trials reported no significant difference between GMAA and conventional treatment with corticosteroids.

The aim of the study was to investigate the usefulness of GMAA for patients with active UC compared with corticosteroids. Moreover, we also evaluate GMAA regimens that are useful for the treatment of UC as a sub-analysis.

2. Materials and methods

2.1. Search strategy

A search of the medical literature was conducted using MEDLINE, the Cochrane controlled trials register (up to January 2012) and the abstract books of recent international congresses, such as Digestive Disease Week 2012, 2013, and 8th Congress of European Crohn's and Colitis Organization, to identify comparative studies of GMAA in patients with UC. The search terms "apheresis" and "adsorption" were used in combination with "inflammatory bowel disease" and "ulcerative colitis". All abstracts were retrieved from the database according to this strategy.

2.2. Inclusion criteria

Only randomized control trials were included. The populations of these studies comprised patients with active UC. Studies included at least two arms: a conventional group treated with corticosteroids and a GMAA group. Moreover, studies comparing GMAA regimens were included for subanalysis; for example, more than 10 GMAA sessions vs. 5 GMAA sessions, and intensive GMAA regimens (≥2 sessions per week) vs. weekly GMAA regimens (1 session per week). Papers were included if they provided information on at least one of the following outcome parameters: clinical response rate, clinical remission rate, clinical disease activity index, steroid-sparing effect, endoscopic findings, histological findings, number of adverse events, and withdrawals.

2.3. Data extraction

Data were extracted independently by two reviewers, including author, year, location of trial, trial design, population of studies, number of subjects enrolled, variety of GMAA preparations, dose administered, and study quality.

2.4. Assessment of bias

Risk of bias was assessed independently by two investigators as described in the Cochrane handbook by recording the method used to generate the randomization schedule, the method used to conceal allocation, whether blinding was implemented, the proportion of patients who completed follow-up, whether an intention-to treat analysis was extractable, and whether there was evidence of selective reporting of outcomes.

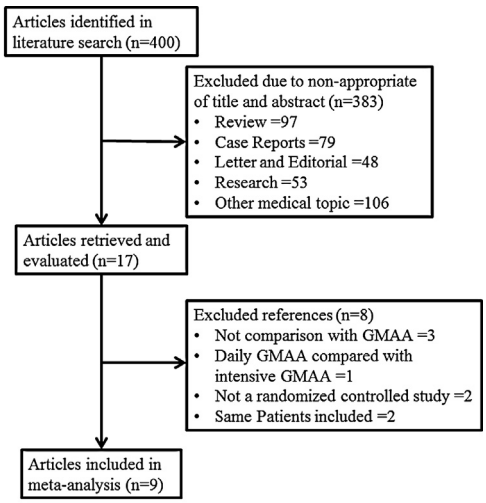

Fig. 1. Literature screening and selection process. The search strategy identified a total of 400 citations. 383 of the 400 citations were excluded and the remaining 17 were retrieved and evaluated in more detail. Of 17 studies, 9 were included in this meta-analysis. GMAA; granulocytes and monocyte adsorption apheresis.

2.5. Statistical analysis

A meta-analysis was performed using Review Manager 5.1 (Cochrane Collaboration, Oxford, CA, USA). The outcome measure examined was the odds ratios (ORs) of the clinical remission rate or clinical response rate and the ratio of adverse events with GMAA vs. corticosteroids by intention-to-treat analysis. Moreover, the outcome measure also examined the ORs of the clinical remission rate with more than 10 GMAA sessions vs. 5 sessions, and intensive GMAA vs. weekly GMAA. The heterogeneity of these studies was assessed using the Chi-squared test. Forest plots were created for graphic display of the results. The size of a box indicates the relative weight of the respective study, while the line gives the 95% confidence interval (95% CI). For the meta-analysis result, the diamond represents the 95% CI. Publication bias was assessed graphically using funnel plots. A funnel plot allows evaluation of possible publication bias by examining the distribution of the effect size of the OR.

3. Results

3.1. Description of studies

The search strategy identified a total of 400 citations (Fig. 1). 383 of the 400 citations were excluded (Review: 97, Case Reports: 79, Letter and Editorial: 48, Basic Research: 53, and other medical topics: 106). The remaining 17 articles were retrieved and evaluated in more detail. Of the 17 studies, 9 were included. The characteristics of these 9 studies were summarized in Table 1. Of these 9, 4 studies compared GMAA with corticosteroids [22,24–26], one study was a sham-controlled double-blinded randomized trial [27], 2 studies compared more than 10 GMAA sessions vs. 5 GMAA sessions [28,29], and the remaining 2 studies compared an intensive GMAA regimen (≥2 sessions per week) vs. a weekly GMAA regimen (1 session per week) [30,31]. Moreover, 4 studies compared the rate of adverse events between GMAA and corticosteroids [22,24,26,27]. Of the 17 studies, 8 were excluded, because 3 made no comparison with GMAA, one paper alone compared daily GMAA with intensive GMAA, 2 were not randomized studies, and whether or not the same patients were included in other studies was unclear in the remaining 2.