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Alimentary Tract

Treatment of patients with acute ulcerative colitis: Conventional corticosteroid therapy (MP) versus granulocytapheresis (GMA): A pilot study

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Abstract

Aim. The aim of our pilot study is to report the efficacy of granulocytapheresis in patients with acute ulcerative colitis with respect to the use of conventional corticosteroids such as methylprednisolone.

Methods. The activity of disease was evaluated by clinical activity index and endoscopic index. Forty patients with acute ulcerative colitis were randomly divided in two groups of 20 subjects each: one group was treated with five sessions of granulocytapheresis, the other one with methylprednisolone for 5 weeks. Complete response was defined as clinical activity index lower than 6 and endoscopic index lower than 4 after 6 weeks of follow-up. Partial response was defined as clinical activity index lower than 6 but endoscopic index more than 4 after 6 weeks of follow-up. All the conditions not included are classified as nonresponders.

Results. All the patients completed the trial. Complete clinical response was observed in 70% of patients treated with granulocytapheresis versus 60% of patients treated with methylprednisolone. A partial response was observed in 20% of patients treated with granulocytapheresis versus 15% of patients treated with methylprednisolone. During the sessions of granulocytapheresis only a transient mild headache was recorded in 10% of patients, while side effects were more common (50%) in the patients treated with methylprednisolone.

Conclusion. Granulocytapheresis represents a new and promising approach to active ulcerative colitis. In fact, even if more expensive than conventional corticosteroids, it seems slightly more effective and, above all, with side effects much less frequent and serious. Thus, granulocytapheresis cycles could be prolonged or repeated, if necessary, in more severe diseases without significant risks for the patients.

Keywords: Acute ulcerative colitis; Granulocytapheresis; Methylprednisolone

1. Introduction

The administration of corticosteroids is generally reserved to patients with moderate to severe ulcerative colitis (UC) or in patients with milder disease who failed to respond to first-line therapies such as mesalamine [1–4].

Even if the use of steroid drugs is a common strategy for the treatment of acute inflammatory bowel diseases (IBDs), large doses of steroids are often necessary to control active diseases and some patients do not respond even to such doses. So, the efficacy of these medications is limited by frequent side effects due to higher dosages and prolonged therapies, and by the presence of a considerable number of nonresponders [2,3]. The additional use of more selective immunosuppressant drugs, such as azathioprine, 6-mercaptopurine and cyclosporine [5–9], helps to reduce the steroid requirements but the overall spectrum still remains unsatisfactory. So, new therapeutic approaches are needed to improve the clinical outcome of patients with acute UC.

In recent years some trials have suggested that granulocytapheresis (GMA) could be a useful and safe way to induce clinical remission in patients with active IBDs, but this new therapy has usually been evaluated only in patients

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"nonresponders" to conventional steroid therapy and often without a control group [10–19]. Thus, the real usefulness and the clinical need of GMA in acute UC it is not clear.

The aim of our trial was a pilot study where we evaluated the efficacy of GMA in patients with acute UC with respect to the use of conventional corticosteroids such as methylprednisolone (MP).

2. Patients and methods

We included in the trial 40 patients with UC lasting 1 year at least, and with current signs of acute disease involving the entire colon in spite of continuous maintenance therapy with mesalamine (5-ASA).

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethical Committee of our hospital. Each recruited patient gave written informed consent before entry.

The diagnosis of UC was made by clinical, endoscopic and histologic data. The activity of the disease was evaluated by clinical activity index (CAI) and endoscopic index (EI) [1,20]. These systems consist of giving the patients a score regarding some fixed clinical signs and colonoscopic findings. Clinical signs included: general wellbeing, abdominal pain, rectal bleeding, number of bowel movements per week, temperature centigrade, possible complications, ESR and blood haemoglobin concentration. Endoscopic evaluation was performed considering: vascular pattern, granularity of mucosal surface, vulnerability of the mucosa and mucosal damage (exudate, erosions, ulcers). We assumed values of CAI $\geq$6 and EI >4 as criteria of clinical activity.

The colonoscopy performed just before the enrolment enabled us to evaluate the colonic extent of the disease: to obtain a homogeneous group, we included in our trial only the patients with UC involving the entire colon (ulcerative pancolitis).

Exclusion criteria were: pregnancy, allergy to heparin, smokers, serious cardiovascular diseases, left-sided or distal colitis, use of topical therapy, UC cases lasting less than 1 year prior the study, diagnosis of steroid-dependant or resistant UC, actual treatment with immunosuppressant drugs.

The characteristics of enrolled patients are shown in Table 1. The patients were randomly divided in two groups, A and B, respectively. The patients in group A received a five session (1 session/week) treatment with GMA. This is an extracorporeal procedure in which 1.8 L of blood are filtered through an Adacolumn^{TM} (JIMRO, Takasaki, Japan). Adacolumn^{TM} is a 335 mL capacity column filled with 35,000 cellulose diacetate beads (2 mm in diameter) that binds granulocytes and monocytes via the CR3 receptors present on these cells. Each apheresis procedure requires the addition of 1500 UI of sodium heparine as an anticoagulant. Blood is obtained by antecubital vein puncture. Haemograms, biochemistry and coagulation were recorded during apheresis treatment.

Table 1
Characteristics of patients

	A	B
Number of patients	20	20
Age (years ± S.D.)	40 ± 6	34 ± 8
Male/female	8/12	11/9
Previous therapy 2.4 g/day of mesalamine	20	20
Previous surgical therapy	0	0
Extraintestinal complications	0	0
Disease duration (years ± S.D.)	5 ± 1	5 ± 2
Months of remission before study entry	5 ± 2	4 ± 1
Extent of disease pancolitis	20	20
CAI (mean ± S.D.)	8 ± 2	9 ± 1
EI (mean ± S.D.)	9 ± 1	11 ± 2

Group A: patients treated with GMA.
Group B: patients treated with MP.
N.S.: not significant.

The patients in group B were treated with i.v. or i.m. MP at dosage of 0.8–1 mg/kg/day for 2 weeks, thereafter such therapy was gradually tapered by 4–6 mg/week if biochemical and clinical findings (CAI lower than 6) showed an improvement of the disease. Otherwise, the initial dosage was maintained as long if clinical findings (CAI lower than 6) did not modify significantly.

Concomitant therapy with oral 5-ASA (Eudragit-S-coated Mesalamine) 2.4 g/day in a delayed-release formulation was maintained in the two groups of patients during the trial.

The therapeutic response was evaluated, in each patient of group A and B, by CAI scoring before the enrolment, every week during the trial and, finally, at 6th week, that is 1 week after GMA discontinuation. The endoscopic pattern was evaluated by EI scoring before the enrolment and at 6th week. We assumed values of CAI lower than 6 and EI lower than 4 as criteria of clinical remission, so a complete response was defined as CAI and EI scores lower than 6 and 4, respectively, at the 6th week of the trial. Partial response was defined as CAI lower than 6 but EI more than 4, 6 weeks after the enrolment. All the conditions not included here, have been classified as nonresponders.

Patients were instructed to notify the investigators if symptoms of active disease occurred before the scheduled visit, and diary cards were given for recording symptoms.

Tolerability of GMA or MP were evaluated on the basis of incidence, as well as type and severity, of side effects occurring during the entire study period.

Even if the sample size was too much small to show a significant difference between the two treatment options a statistical analysis for homogeneity of the two groups with respect to age, sex, previous therapies and clinical signs. A comparison between the patients treated with GMA or MP was performed using the Chi-square test and Fisher's exact test, as appropriate, and Student's *t*-test for comparison of mean ± S.D. at the end of the study was performed by the long rank test at 95% confidence interval. All statistical tests were