Journal of Crohn's and Colitis (2014) 8, 981–991

Available online at www.sciencedirect.com

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A large-scale, prospective, observational study of leukocytapheresis for ulcerative colitis: Treatment outcomes of 847 patients in clinical practice

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Received 25 December 2013; received in revised form 29 January 2014; accepted 29 January 2014

Abbreviations: 5-ASA, 5-aminosalicylic acid; CAI, Clinical Activity Index; CRF, case report form; CRP, C-reactive protein; CyA, cyclosporine; DAI, Disease Activity Index; GMA, granulocyte and monocyte adsorptive therapy; GPSP, Good Postmarketing Study Practice; IBD, inflammatory bowel disease; IFX, infliximab; LCAP, leukocytapheresis; MedDRA, Medical Dictionary for Regulatory Activities; Tac, tacrolimus; UC, ulcerative colitis.

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1873-9946
http://dx.doi.org/10.1016/j.crohns.2014.01.027

KEYWORDS
Ulcerative colitis;
Leukocytapheresis;
Large-scale observational study;
Safety;
Treatment outcomes

Abstract

Background and aims: Leukocytapheresis is an extracorporeal therapy for ulcerative colitis. However, no large-scale study on leukocytapheresis has been reported. This large-scale, prospective, observational study aimed to evaluate the treatment outcomes of leukocytapheresis for active ulcerative colitis in clinical practice.
Methods: Patients with active ulcerative colitis treated with leukocytapheresis using a Cellsorba E column between May 2010 and December 2012 were enrolled from 116 medical facilities in Japan.
Results: A total of 847 patients were enrolled, and 623 were available for efficacy analysis. Out of 847 patients, 80.3% of the patients had moderate to severe disease activity, and 67.6% were steroid refractory. As concomitant medications, 5-aminosalicylic acids, corticosteroids, and thiopurines were administered to 94.8%, 63.8%, and 32.8% of the patients, respectively. In addition, infliximab and tacrolimus were concomitantly used in 5.8% and 12.3%, respectively. Intensive leukocytapheresis (≥ 4 leukocytapheresis sessions within the first 2 weeks) was used in $>70\%$ of the patients. Adverse events were seen in 10.3% (87/847), which were severe in only 5 patients (0.6%). Any concomitant medications did not increase the incidence of adverse events. Intensive leukocytapheresis was as safe as the conventional weekly procedure. The overall clinical remission rate was 68.9% (429/623), and the mucosal healing rate was 62.5% (145/232). Clinical remission was achieved more frequently and rapidly in the intensive group than in the weekly group.
Conclusions: This large-scale study indicates that leukocytapheresis, including intensive procedure, is a safe and effective therapeutic option for active ulcerative colitis.

1. Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease that mainly affects the mucosa of the colon, causing erosion and ulceration.[1] UC is a chronic disease with repeated relapses and remissions; its typical clinical symptoms include bloody stools and abdominal pain. Although the etiology of UC is not fully understood, inflammatory cytokines produced by leukocytes (including neutrophils, monocytes, and lymphocytes) that infiltrate the mucosa of the intestine are considered key factors in the pathogenesis of the condition.[2,3]

Conventional medications for active UC typically include the use of 5-aminosalicylic acid (5-ASA),[4,5] but corticosteroids are often used in patients refractory to 5-ASA.[6,7] Corticosteroids are effective in many patients, but their long-term use may result in various adverse effects, including Cushingoid facies, infections, and osteoporosis.[8] Therefore, long-term use of corticosteroids should be limited.

Leukocytapheresis (LCAP) using a Cellsorba E column (Asahi Kasei Medical Co., Ltd., Tokyo, Japan), which is filled with nonwoven polyester fiber, is a blood purification therapy that exerts anti-inflammatory effects by removing activated leukocytes or platelets from the peripheral blood through an extracorporeal circulation.[9–12] An open-label multicenter randomized control study showed that LCAP with low-dose corticosteroids (26.9 mg/day on average) in the treatment of active UC had significantly higher efficacy (29/39, 74%) than high-dose corticosteroids (47.9 mg/day on average; 14/37, 38%) and had significantly lower (24%) incidence of adverse events than high-dose steroid treatment (68%).[13] In a multicenter, double-blind, prospective, case–control study with sham apheresis as placebo treatment, the response rate with LCAP was 80% in 19 patients with active UC, which was significantly higher than that in the sham group.[14] Recently, LCAP has been shown to be effective not only in the improvement of clinical symptoms but also in the induction of mucosal healing.[15] However, the numbers of subjects in these studies were small and no large-scale study evaluating the efficacy and safety of LCAP has been conducted.

Recently, biological drugs such as infliximab (IFX) and immunosuppressive drugs such as tacrolimus (Tac) have been used for treating UC.[16–18] The efficacy and safety of LCAP with concomitant use of these drugs has not been reported. Furthermore, in Japan, patients were previously only allowed to receive LCAP once per week. However, the revision of public insurance coverage in 2010 removed the restrictions on the frequency of LCAP and has enabled patients to receive ≥ 2 LCAP treatments per week (referred to as intensive LCAP) in clinical practice. However, the safety and efficacy of intensive LCAP have not been reported in the literature. Therefore, we conducted a large-scale, prospective, observational, postmarketing study to evaluate the treatment outcomes of LCAP, including intensive LCAP, as currently used in clinical practice.

2. Materials and methods

2.1. Study design

This postmarketing study was conducted in accordance with the Good Postmarketing Study Practice (GPSP) ordinance of the Japanese Ministry of Health, Labour and Welfare. The GPSP ordinance is the authorized standard for postmarketing studies of approved drugs and medical devices in clinical practice.

Patients were recruited from 116 medical facilities in Japan between May 2010 and December 2012. To eliminate any selection bias, a continuous registration method was