New Horizon

Leukocyte Apheresis in the Management of Ulcerative Colitis
Ahmed Helmy, Maheeba Abdulla, Ingvar Kagevi, Khalid Al Kahtani

ABSTRACT

Ulcerative colitis is a chronic inflammatory disease that affects the colon and rectum. Its pathogenesis is probably multifactorial including the influx of certain cytokines into the colonic mucosa, causing disease activity and relapse. The hypothesis of removing such cytokines from the circulation by leukocytapheresis was implemented to reduce disease activity, maintain remission, and prevent relapse. Many recent reports not only in Japan, but also in the West, have highlighted its beneficial effects in both adult and pediatric patients. Large placebo-controlled studies are needed to confirm the available data in this regard. In this article, we shed some light on the use of leukocyte apheresis in the management of autoimmune diseases, especially ulcerative colitis.

Key Words: Cytapheresis, granulocytapheresis, therapy, inflammatory bowel disease, induction of remission

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) with a relapsing and remitting course. It affects many individuals worldwide with deleterious effects on the quality of life. Many medications, including anti-inflammatory drugs, corticosteroids, immunosuppressive drugs, and biological agents, are used to induce and maintain remission without curing the disease and with many side effects.

The pathogenesis of UC is ill-understood, and seems to result from a complex interplay between susceptibility genes, environmental factors, and the immune system. Many inflammatory cytokines, such as tumor necrosis factor (TNF-α), interleukin (IL)-1β, IL-6, IL-8, and others are involved. The sources of these cytokines are the activated peripheral blood granulocytes which get mobilized first, then infiltrate the colonic mucosa and interact with lymphocytes to orchestrate the inflammatory response and initiate disease activity and/or relapse. Therefore, removal of these activated granulocytes by extracorporeal cytapheresis systems, i.e., leukocytapheresis and granulocytapheresis may be a logical therapeutic maneuver.

The goal of this concise report is to present the available data on the efficacy, safety, and applicability of cytapheresis in patients with UC.

DEFINITION

Cytapheresis is an extracorporeal removal of specific cells from the blood using special filters or columns. Due to its ability to remove white blood cells, cytapheresis has been used as a therapeutic modality in many diseases in which sensitized white cells have a pathogenic effect. Leukocytapheresis and granulocytapheresis were mainly used in Japan, but over the last decade, they have also attracted much attention in Europe and North America.

SYSTEMS

Cellsorba (Asahi Medical, Tokyo, Japan) and Adcolumn (Japan Research Laboratories, Takasaki, Japan, Figure 1) are the commonly used apheresis systems in the current literature. The whole venous blood is perfused through an adsorption column. The blood is pumped from a peripheral vein in one arm, filtered, and returned to the body via the other arm. A total of 1800 mL blood is filtered over a period of 60 min. The device which uses an Adacolumn filter is preferred over the Cellsorba filter as it selectively removes activated granulocytes and monocytes with no significant change in the number of lymphocytes or platelets.

CLINICAL USES

The beneficial effect of Adacolumn is related to its ability to reduce numbers of granulocytes, monocytes, and inflammatory cytokine levels (TNF-α, IL-1β, IL-6, and IL-8). Additionally, the Adacolumn increases the concentration of circulating immature neutrophils and reduces their ability to secrete such pro-inflammatory cytokines.
was first used in Japan for treating patients with leukemia in the 1980s, and is currently used in several autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and IBD with varying degrees of success [Table 1]. In UC, cytapheresis is indicated in patients with moderately severe cases (steroid-resistant or naïve cases), intractable disease (steroid-dependent), and in severe or fulminant disease.\(^{[17]}\)

**ADVANTAGES**

The principle of cytapheresis is to remove badly programmed cells instead of adding medications; this explains its relative safety. Cytapheresis does not require shunt operation, as in chronic hemodialysis, does not exacerbate anemia, nor does it influence hemodynamic parameters.\(^{[18,19]}\) Each apheresis session lasts for 60 min and can be done in an outpatient setting. Also, it has good tolerability as each treatment course for UC consists of a single session per week for five weeks. In addition, it may improve patients’ quality of life.\(^{[2]}\) It should be noted that cost-effectiveness has not been studied in this type of patients. Leukopheresis for IBD has not been recommended by US-FDA as first-line or even second-line treatment until now.

**DISADVANTAGES**

Most of the adverse effects are mild and transient and are attributed to the extracorporeal circulation. These include dizziness, headache, fever, chills, nausea, vomiting, and abdominal pain. In addition, apheresis is a costly procedure compared to other therapeutic modalities. However, it is cost-effective as it reduces the number of hospital admissions, the treatment for steroid-induced side-effects, the need for the expensive biological therapies, and/or the need for surgery.\(^{[17]}\)

**EFFICACY IN UC**

Many studies have been conducted to evaluate the efficacy of cytapheresis in the induction of remission in patients with IBD [Table 2].\(^{[19-42]}\) Most of these studies were conducted in small numbers of patients with variable disease severity, and were open-label, uncontrolled studies; a few were randomized.\(^{[22,23,33]}\) However, they all supported the effectiveness of cytapheresis in reducing disease activity, achieving clinical remission, and enhancing mucosal healing. Interestingly, cytapheresis in pediatric patients has similar effectiveness in inducing as well as maintaining remission in steroid refractory UC as in adults. This can reduce the serious steroid-related complications such as growth retardation, infection, and cosmetic effects.\(^{[26-28]}\)

**REGIMENS**

Standard (conventional) course: One session per week for five consecutive weeks.

Intensive course: 2–3 sessions per week in the first two weeks, then once weekly. An intensive cytapheresis course induces rapid remission and is, therefore, a preferred regimen compared to the standard once-weekly course.\(^{[23,42]}\)

**POTENTIAL ROLE OF PHOTOPHERESIS**

Extracorporeal photopheresis (ECP) is the ex vivo exposure of apheresed peripheral blood mononuclear cells to ultraviolet A light in the presence of a DNA-intercalating agent such as 8-methoxypsoralen (8-MOP), and their subsequent reinfusion. ECP was used initially since the early 1980s in managing malignant and autoimmune diseases including...
Sezary syndrome, T-cell lymphoma, and graft-versus-host disease. In ECP, exposure of circulating immune cells to UVA and 8-MOP induces immunomodulatory changes that lead to tolerance to alloreactive or autoreactive antigen-generated T-cell responses. The potential role of ECP in combination with apheresis in patients with IBD has not been tested, and warrants further investigation.

CONCLUSIONS

Cytapheresis may offer an adjuvant therapeutic option for inducing and maintaining remission in patients with chronic active UC. It is associated with a low incidence of adverse effects compared to other modalities. Well-designed placebo-controlled trials as definitive proofs of efficacy are currently underway. Also needed are studies addressing optimal treatment schemes, patients who would benefit most from this modality, when to combine it with other therapies such as immunotherapy, and the value of using ECP.

REFERENCES

1. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004;126:1504-17.
2. Oxelmark L, Hillerås P, Dignass A, Mössner J, Schreiber S, Kruis W, et al. Quality of life in patients with active ulcerative colitis treated with selective leukocyte apheresis. Scand J Gastroenterol 2007;42:406-7.
3. Taffet SL, Das KM. Sulfasalazine. Adverse effects and desensitization.
Leukocytapheresis (LCAP) in the management of chronic active bowel disease: the first 100 patients treated in Scandinavia. Scand J Gastroenterol 2003;28:833-42

4. Present DH. How to do without steroids in inflammatory bowel disease? Inflamm Bowel Dis 2000;6:48-57.

5. Schreiber S, Nikolaus S, Hampe J, Hämling J, Koop I, Groessner B, et al. Tumour necrosis factor alpha and interleukin 1beta in relapse of Crohn's disease. Lancet 1999;353:459-61.

6. Papadakis KA, Targan SR. Role of cytokines in the pathogenesis of inflammatory bowel disease. Annu Rev Med 2000;51:289-98.

7. Kanai T, Makita S, Kawamura T, Nemoto Y, Kubota D, Nagayama K, et al. Extracorporeal elimination of TNF-alpha-producing CD14(dull)/CD16(+) monocytes in leukocytepheresis therapy for ulcerative colitis. Inflamm Bowel Dis 2007;13:284-90.

8. Nikolaus S, Bauditz J, Gionchetti P, Witt C, Lochs H, Schreiber S. Increased secretion of pro-inflammatory cytokines by circulating polymorphonuclear neutrophils and regulation by interleukin 10 during intestinal inflammation. Gut 1998;42:470-6.

9. Tibble JA, Sigthorsson G, Bridger S, Fagerhol MK, Bjarnason I. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. Gastroenterology 2000;119:15-22.

10. Lugerina N, Kashikari T, Stoll R, Domuschke W. Current concept of Helmy, et al. Leukocyte adsorptive apheresis for active ulcerative colitis. J Gastroenterol 2008;43:51-6.

11. Wilder RL, Malone DG, Yarboro CH, Berkebile C, Haraoui B, Allen JB, et al. Inflammatory bowel disease: the first 100 patients treated in Scandinavia. Scand J Gastroenterol 2003;35:459-61.

12. Suemitsu J, Yoshida M, Yamawaki N, Yamashita Y. Leukocytapheresis therapy by extracorporeal circulation using a leukocyte removal filter. Ther Apher 1998;2:112-8.

13. Suenmits J, Yoshida N, Yamawaki N, & Yamashita Y. Leukocytapheresis therapy by extracorporeal circulation using a leukocyte removal filter. Ther Apher 1998;2:31-6.

14. Hanai H, Saniabadi AR, Komuka S, Hirata I, Adachi M, Agishi T, et al. Granulocytapheresis in the treatment of patients with rheumatoid arthritis. J Clin Apher 1984;2:123-8.

15. Hanai H, Saniabadi AR,Komuka S, Hirata I, Adachi M, Agishi T, et al. Granulocytapheresis in the treatment of patients with rheumatoid arthritis. Artif Organs 1997;2:989-94.

16. Saniabadi AR, Hanai H, Takeuchi K, Umemura K, Nakashima M, Adachi T, et al. Adacolumn, an adsorptive carrier granulated monocytes and monocyte apheresis device for the treatment of inflammatory and refractory diseases associated with leukocytes. Ther Apher 2003;7:48-59.

17. Hanai H, Watanabe F, Saniabadi AR, Matsushitai I, Takeuchi K, Iida T. Therapeutic efficacy of granulocyte and monocyte adsorption apheresis in severe active ulcerative colitis. Dis Sci 2002;47:2349-53.

18. Kashiwagi N, Sugimura K, Koiwai H, Yamamoto H, Yoshikawa T, Saniabadi AR, et al. Immunomodulatory effects of granulocyte and monocyte adsorption apheresis as a treatment for patients with ulcerative colitis. Dig Dis Sci 2002;47:1334-41.

19. Yamamoto T, Umeage S, Matsumoto K. Safety and clinical efficacy of granulocyte and monocyte adsorptive apheresis therapy for ulcerative colitis. World J Gastroenterol 2006;12:520-5.

20. Miyamoto H, Okahisa T, Iwaki H, Murata M, Ito S, Nitta Y, et al. Influence of leukocytepheresis therapy for ulcerative colitis on anemia and hemodynamics. Ther Apher Dial 2007;11:16-21.

21. Ljung T, Thomsen OØ, Vatn M, Karlén P, Karlson LN, Tysk C, et al. Extracorporeal elimination of TNF-alpha-producing CD14(dull)/CD16(+) monocytes in leukocytepheresis therapy for ulcerative colitis. Inflamm Bowel Dis 2007;13:284-90.

22. Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, Kageoka M, et al. Intensive granulocyte and monocyte adsorption versus intravenous prednisolone in patients with severe ulcerative colitis: An unblinded randomised multi-centre controlled study. Dig Liver Dis 2008;40:433-40.

23. Takemoto K, Kato J, Kuriyama M, Nawa T, Kureome M, Okada H, et al. Predictive factors of efficacy of leukocytepheresis for steroid-resistant ulcerative colitis patients. Dig Liver Dis 2007;39:422-9.

24. Okada H, Takenaka R, Hiraoka S, Makidono C, Hori S, Kato J, et al. Centrifugal leukocytapheresis therapy for ulcerative colitis without concurrent corticosteroid administration. Ther Apher Dial 2006;10:242-6.

25. Sakuraba A, Sato T, Naganuma M, Morohoshi Y, Matsuoka K, Inoue N, et al. A pilot open-labeled prospective randomized study between weekly and intensive treatment of granulocyte and monocyte adsorption apheresis for active ulcerative colitis. J Gastroenterol 2008;43:51-6.

26. Naganuma M, Funakoshi S, Sakuraba A, Takagi H, Inoue N, Ogata H, et al. Granulocytapheresis is useful as an alternative therapy in patients with steroid-refractory or -dependent ulcerative colitis. Inflamm Bowel Dis 2004;10:251-7.

27. Domènech E, Hinojosa J, Esteve-Comas M, Gomollón F, Herrera JM, Bastida G, et al. Granulocyte apheresis in steroid-dependent inflammatory bowel disease: a prospective, open, pilot study. Aliment Pharmacol Ther 2004;20:1347-52.

28. Kim HJ, Kim JS, Han DS, Yang SK, Hahn KB, Lee WJ, et al. Granulocyte and monocyte apheresis for active ulcerative colitis: treatment for steroid refractory patients with active ulcerative colitis: a prospective open-label multicenter study. Korean J Gastroenterol 2005;45:34-44.
38. Sawada K, Kusugami K, Suzuki Y, Bamba T, Munakata A, Hibi T, et al. Leukocytapheresis in ulcerative colitis: results of a multicenter double-blind prospective case-control study with sham apheresis as placebo treatment. Am J Gastroenterol 2005;100:1362-9.
39. Kruis W, Dignass A, Steinhagen-Thiessen E, Morgenstern J, Mössner J, Schreiber S, et al. Open label trial of granulocyte apheresis suggests therapeutic efficacy in chronically active steroid refractory ulcerative colitis. World J Gastroenterol 2005;11:7001-6.
40. D’Ovidio V, Aratari A, Viscido A, Marcheggiano A, Papi C, Capurso L, et al. Mucosal features and granulocyte-monocyte-apheresis in steroid-dependent/refractory ulcerative colitis. Dig Liver Dis 2006;38:389-94.
41. Sands BE, Sandborn WJ, Wolf DC, Katz S, Safdi M, Schwartz DA, et al. Pilot feasibility studies of leukocytapheresis with the Adacolumn Apheresis System in patients with active ulcerative colitis or Crohn’s disease. J Clin Gastroenterol 2006;40:482-9.
42. Aoki H, Nakamura K, Yoshimatsu Y, Tsuda Y, Irie M, Fukuda K, et al. Adacolumn selective leukocyte adsorption apheresis in patients with active ulcerative colitis or Crohn’s disease. J Clin Gastroenterol 2006;40:482-9.
43. McKenna KE, Whittaker S, Rhodes LE, Taylor P, Lloyd J, Ibbotson S, et al. Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. Br J Dermatol 2006;154:7-20.
44. Gasová Z, Spísek R, Dolezalová L, Marinov I, Vítek A. Extracorporeal photochemotherapy (ECP) in treatment of patients with c-GVHD and CTCL. Transfus Apher Sci 2007;36:149-58.
45. Zane C, Venturini M, Sala R, Calzavara-Pinton P. Photodynamic therapy with methylaminolevulinate as a valuable treatment option for unilesional cutaneous T-cell lymphoma. Photodermatol Photoimmunol Photomed 2006;22:254-8.
46. Couriel DR, Hosing C, Saliba R, Shpall EJ, Anderlini P, Rhodes B, et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood 2006;107:3074-80.
47. Gorgun G, Miller KB, Foss FM. Immunologic mechanisms of extracorporeal photochemotherapy in chronic graft-versus-host disease. Blood 2002;100:941-7.
48. Osella-Abate S, Zaccagna A, Savoia P, Quaglino P, Salomone B, Bernengo MG. Expression of apoptosis markers on peripheral blood lymphocytes from patients with cutaneous T-cell lymphoma during extracorporeal photochemotherapy. J Am Acad Dermatol 2001;44:40-7.

**Source of Support:** Nil, **Conflict of Interest:** None declared.