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Leukocytapheresis in Ulcerative Colitis: A Possible Alternative to Biological Therapy?

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Inflammatory bowel disease (IBD) is a chronic relapsing and remitting digestive disorder that includes both Crohn's disease and ulcerative colitis. The underlying cause of IBD remains unclear but is thought to involve an inherent defect in the innate immune system, possibly a breach in epithelial barrier function, which disrupts the delicate homeostatic balance achieved between commensal bacteria residing in the gut and immunosurveillance mechanisms of the mucosal immune system. The result is an overly aggressive adaptive immune response against the commensal flora or other antigens that involves massive recruitment of leukocytes into the affected intestinal tissues, inflammation, and tissue damage.

Given that the exact pathological mechanisms underlying IBD are unknown, therapeutic strategies have been developed to treat the apparent symptoms of disease rather than the underlying cause of disease. Patients with ulcerative colitis have traditionally been treated with generalized anti-inflammatory medications such as 5-aminosalicylates and corticosteroids with significant success. However, a substantial number of patients either lose their response to corticosteroids (steroid refractory) or are unable to taper off corticosteroids without disease recurrence (steroid dependent). In addition, extended use of corticosteroids is associated with significant side effects. In recent years, biological agents have been developed that more specifically target the proposed underlying pathogenic mechanisms of disease. The most successful example has been infliximab, which is a monoclonal antibody infusion therapy that targets the proinflammatory cytokine TNF α . In randomized clinical trials, 69% of steroid refractory ulcerative colitis patients experienced a clinical response to infliximab 1. However, the long-term effects of blocking TNF α are unknown, and several serious side effects have been reported with the use of biological therapy, including serious infections and possible lymphoma 2. As a result of these therapeutic limitations, many patients with steroid-dependent or steroid refractory ulcerative colitis end up undergoing a total colectomy. Clearly, more effective medical therapies with fewer side effects would greatly enhance the health-related quality of life for these patients.

Currently, two selective adsorption apheresis devices are approved for use in Japan and Europe, including Cellsorba leukocytapheresis column and the Adacolumn adsorptive extracorporeal granulocyte-monocyte apheresis device. In this issue of the Journal, Hibi et al. present the results of a large post-marketing study of the Adacolumn (Japan Immunoresearch Laboratores Co., Ltd), a leukocytapheresis column that selectively adsorbs granulocytes and monocytes extracorporeally from the peripheral blood of patients

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with ulcerative colitis. The aim of the study was to further assess the safety and efficacy of granulocyte and monocytes apheresis (GMA) using the Adacolumn in a large cohort of patients with active ulcerative colitis. The study followed 697 patients who received a total of 5,287 GMA sessions at 53 centers in Japan over a period of seven years. Patients were assessed before receiving GMA and two weeks post GMA; no long term follow-up was performed. At the time of enrollment, 92% of patients were being treated with aminosalicylates, 74% of patients were on corticosteroids, and 9% of patients were receiving other immunomodulatory medications. No serious adverse events were reported in association with the use of GMA, and mild or moderate adverse events were reported in 7.7% of the 697 patients studied, suggesting that the Adacolumn is indeed a safe intervention for patients with active ulcerative colitis.

In accordance with the guidelines for post-marketing studies from the Japan Ministry of Health, 656 of the 697 patients enrolled were available for evaluation of efficacy. Of these 656 patients, 77.3% experienced a clinical response to GMA, and 71.1% experienced a clinical remission. Since a long-term follow-up was not performed, no data are available of the time to relapse in these patients. Moreover, although these data were collected from a relatively large study cohort, it is important to note that this is a post-marketing study that lacks randomization or a control group. Although 70% of the study cohort was classified as having refractory UC, no data is reported on the duration or dose of steroid use prior to receiving GMA, introducing the possibility that the effect of steroid use may have confounded the reported treatment effect for Adacolumn GMA. In addition, without an adequate control group it is impossible to know the true size of the “placebo effect” that is associated with extracorporeal therapy. That is, some patients may have reported clinical improvements simply because they knew they were being treated, regardless of whether or not the therapy was effective for them. The fact that 69.4% of the subset of 219 patients who underwent endoscopic evaluation had endoscopic grading indices representative of clinical remission would support the notion that the placebo effect in this study was relatively small. However, a randomized, double-blind, sham-controlled study of Adacolumn GMA in patients with moderate to severely active ulcerative colitis by Sands et al. found no difference in clinical remission or response rates between the GMA and sham treatment groups 3. These results suggest the possibility that in an unblinded study extracorporeal therapy alone may incur a placebo effect and thereby inflate the observed treatment effect, regardless of whether or not granulocytes and monocytes are actually adsorbed from the peripheral blood. Finally, patients were administered heparin, low molecular weight heparin, or nafamostat mesolate as an anti-coagulant during their extracorporeal procedure. Although the GMA response rates among patients receiving the different anticoagulant was comparable, it should be noted that low molecular weight heparin itself has been evaluated as a potential therapy for patients with ulcerative colitis. However, a meta-analysis of low molecular weight heparin as well as multiple randomized controlled trials showed no benefit of heparin over placebo or as an adjunct to standard therapy 4–6. These potential confounding effects notwithstanding, Hibi et al. have shown that extracorporeal treatment with the Adacolumn GMA is safe and associated with a very high rate of clinical remission and response in a large cohort of patients with ulcerative colitis.

One important contribution of such a large-scale study is the ability to use the resulting data set to identify parameters that may be predictive of response to therapy. Hibi et al. performed univariate statistical analysis on the 656 patients for whom efficacy data were available and were able to identify hypersensitivity to food and/or drugs as predictive for a poor response to GMA. Multivariable logistical regression also identified baseline granulocyte count as predictive of response to GMA, when controlling for age and duration of disease. These data are useful for targeting Adacolumn GMA toward patients who are likely to benefit from the intervention.

In summary, selective adsorption of granulocytes and monocytes from the peripheral blood of patients with active ulcerative colitis using the extracorporeal Adacolumn GMA appears to be an extremely safe treatment modality. Although conflicting results have been reported regarding the efficacy of Adacolumn GMA, this study by Hibi et al. adds to the existing literature by providing data from the largest population of ulcerative colitis patients yet to be studied. If the observed treatment effect of 77.7% is representative of the true response rate, Adacolumn GMA would be a safe alternative to biological therapies for patients with refractory ulcerative colitis. In addition, granulocyte fractions could be used to help identify patients who are most likely to benefit from this procedure.

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