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Chapter

Apheresis in Inflammatory Bowel Disease: Current Evidence

Balaban Daniel Vasile and Mariana Jinga

Abstract

Inflammatory bowel diseases (IBD) have become a major focus for gastroenterologists worldwide, with the increasing incidence and complexity of cases, which pose therapeutic challenges. Currently available approaches fail in controlling the disease activity in a significant proportion of patients and some of the therapies are associated with significant adverse events. Although new molecules are on the horizon and treatment strategies have been optimized, novel therapeutic tools are much needed in IBD for patients who fail to attain control of the disease. Apheresis is now a common non-pharmacological therapeutic modality used in several pathologies, IBD also. In the current review, we summarize currently available evidence with respect to selective apheresis in IBD.

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, apheresis, leukapheresis

1. Introduction

Inflammatory bowel diseases (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory conditions of the digestive tract with a relapsing-remitting course, which can dramatically decrease patients' quality of life. With a steadily increasing incidence worldwide [1] and with the growing needs and demands from patients, IBD have become a major focus for the gastroenterology community, both practitioners and researchers. Over the last decades, management of IBD has improved considerably, but is quite far from being satisfactory for a significant number of patients. Currently, the therapeutic armamentarium includes several drug regimens, endoscopic therapies, and surgery. Despite the development of novel targeted molecules and optimization of treatment strategies in IBD, some patients fail to achieve disease control with currently available treatment options. Moreover, drug-based therapies are associated with significant adverse events and contraindications, which may lead to treatment discontinuation or even refusal of therapy. Not least, chronic use of conventional therapies is associated with loss of response, which can pose challenges in the long-term control of the disease. In this setting, novel therapeutic approaches have been searched for by the scientific community and apheresis has emerged as a promising non-pharmacologic treatment option in IBD.

Although guidelines are not frequently reporting it [2], several successful experiences have been reported so far in the literature. In this chapter, we will summarize current evidence regarding apheresis in IBD.

2. Principles of apheresis in IBD

Apheresis techniques are being used in many medical specialties, from nephrology and intensive care to gastroenterology. It consists of depleting the patient's blood from certain components (cells, cytokines, or other molecules) depending of the filter used and the indication. Its applications in digestive pathology include alcoholic hepatitis [3], hepatitis C-associated cryoglobulinemia [4], hypertriglyceridemia-induced acute pancreatitis [5], and IBD.

IBD is undoubtedly characterized by complex pathogenesis, but leucocytes play a key role in driving the bowel inflammation. Most of the conventional treatments in IBD address the proinflammatory cytokines released by the activated leucocytes, while apheresis acts by extracting the white cells (specifically a subset of WBCs) from the patient's blood, either by centrifugation or by passing the blood through an adsorptive device. Initially, centrifugation was used to deplete the activated leukocytes from the patient's blood; this reduction in the number of WBCs proved beneficial for IBD patients but had limitations generated from the nonspecific removal of leukocytes. To overcome these limitations, columns containing membrane filters or adsorbing beads have been developed to selectively remove the desired level of WBCs.

Regarding the use of apheresis in IBD, its benefits reside from depleting the blood from certain subtypes of leucocytes, which migrate into the bowel wall and fuel the local inflammatory response. This selective removal of specific white cells—mostly granulocytes and monocytes—is being regarded as a technique of extracorporeal immunomodulation, with proven benefits for IBD patients; besides this selective depletion of granulocytes and monocytes/macrophages, several other beneficial changes in the inflammatory cascade of IBD patients have been reported and could contribute to the efficacy of apheresis in IBD [6].

A schematic description of leukocyte apheresis in IBD is represented in **Figure 1**—the patients' blood is passed through a filter which selectively removes white cells (mainly granulocytes and monocytes) and then returned to the patient's body; the resulting blood has fewer leukocytes and in turn there are (?) less of them to fuel the inflammation in the bowel wall. As for other extracorporeal machines, anticoagulation is used during leukapheresis for IBD.

First reports of apheresis in IBD date back from 1980s [7], when centrifugal leukocytapheresis was used in patients with Crohn's disease. With this technique, the patient's blood was depleted by about 55% of lymphocytes, 40% of granulocytes, and a significant amount of red blood cells and platelets [6].

Subsequent models for apheresis incorporated a filter or a column for the selective removal of certain blood components. Currently, there are two leukocyte adsorptive devices available for apheresis in IBD patients [6, 8]:

- *Adacolumn* (Japan Immunoresearch Laboratory, Japan), a granulocyte/monocyte apheresis (GMA) system which consists of a column filled with cellulose-coated acetate beads that selectively remove granulocytes and monocytes through binding of FCγR (Fc gamma receptor—a receptor for the Fc portion of IgG), and to a lesser extent lymphocytes, as they do not express FCγR [9]. The device adsorbs 65% of granulocytes, 55% of monocytes, and only 2% of lymphocytes and few platelets [10]. Patients usually undergo one or more sessions per week up, according to different protocols.

- *Cellsorba* (Asahi Medical, Japan), a leukocyte apheresis (LCAP) system represented by a column containing non-woven polyester fibers, which retain leucocytes as follows: 90–100% of granulocytes and monocytes, 30–60% of lymphocytes, and a certain amount of thrombocytes [11, 12].

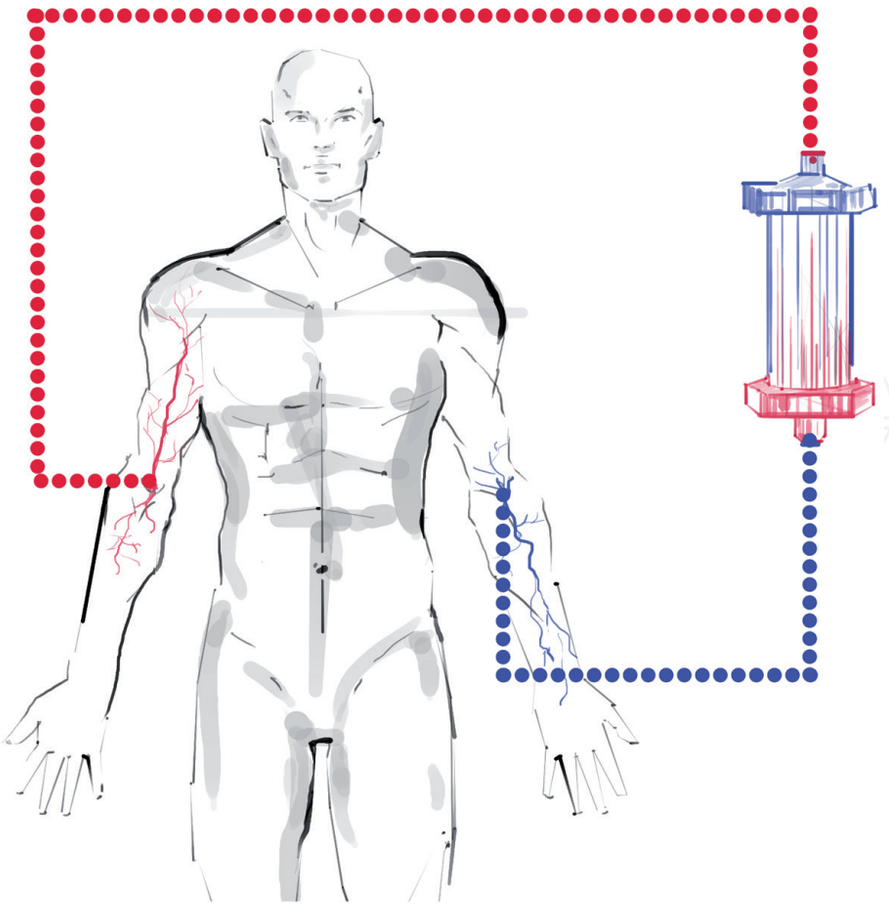

Figure 1.
Schematic representation of apheresis in IBD.

3. Leukapheresis in IBD

Leukocyte apheresis (leukapheresis) has been evaluated in several trials as a treatment option in patients with steroid-dependent or steroid-refractory UC/CD and in moderate-severe disease unresponsive to conventional therapy. The standard protocol implies that the patient has one apheresis session (60 minutes duration) per week for 5–10 consecutive weeks, but others have proposed modified protocols with more intensive therapy (2 sessions per week, 90 minutes duration). Common adverse reactions include dizziness, headache, and mild, transient fever. The procedure has a good safety profile and is usually well tolerated. Leukapheresis allows IBD patients to taper or even get off steroids and to achieve earlier remission [13]. Besides patients with steroid-dependent and steroid-refractory disease, it has proven efficacious in steroid-native patients also. A major issue of leukapheresis is cost, but considering the elimination of the need for steroids and their complications and the need for hospitalization for flaring, this non-pharmacologic technique may be cost-effective for selected patient categories [14]. A selection of studies reporting its efficacy and safety is presented in **Tables 1** and **2**.

Most of the above papers report on the efficacy and safety of apheresis techniques in difficult to treat patient categories—steroid-dependent/-resistant or refractory to conventional treatment, UC being studied more than CD. However, while early observational studies have reported very high response or remission rates (up to 80%) in these difficult to treat patients, a randomized controlled trial comparing GMA to sham (placebo) showed much lower remission rates and no significant differences between the compared groups than in previous studies [36].

Author, year	Indication	No. of patients	Overall response rate	Adverse events (number or %)
Shimoyama et al., 2001 [15]	UC (refractory to conventional treatment)	53	58.5% of patients had remission or improved	9.4%—8 non-severe AE (in 5 patients)
Tomomasa et al., 2003 [16]	Pediatric UC (steroid-refractory)	12	67% improvement	9%
Hanai et al., 2003 [17]	UC	31 steroid-refractory 8 steroid naive	81% remission in steroid-refractory, 88% in steroid-naive	18%
Matsui et al., 2003 [18]	CD (refractory to conventional treatment)	7	71.4%	
Hanai et al., 2004 [19]	UC (steroid-dependent)	46	83% remission at week 12	21.7% (10 mild AE)
Suzuki et al., 2004 [20]	UC (steroid-naive)	20	85% remission	10%
Kusaka et al., 2004 [21]	CD (un-responsive to conventional treatment)	6	66.6%	
Fukuda et al., 2004 [22]	CD (moderate-severe, unresponsive to standard therapy)	21	52.4%	
Naganuma et al., 2004 [23]	UC (steroid-refractory or -dependent)	44	55% remission + 20% clinical response	5%
Yamamoto et al., 2004 [24]	UC (mild-moderate)	30	70% clinical remission	27% (in 8 patients, 9 sessions)
Domenench 2004 [25]	UC and CD	14 (13*) UC, 12 (10*) CD	62% remission in UC, 70% in CD	4
Kanke et al., 2004 [26]	UC (mild to severe)	60	23% remission, 60% improvement	18%
Kim et al., 2005 [27]	UC (refractory to conventional treatment)	27	70% improvement	11%
Kruis et al., 2005 [28]	UC	39 (35*)	37.1% clinical remission and 28.6% endoscopic remission	1
D'Ovidio et al., 2006 [29]	UC (mild-moderate, steroid dependent/ refractory)	12	75% clinical response	None
Ikeda et al., 2006 [30]	Pediatric UC	4	75%	
Sands et al., 2006 [31]	IBD	15 UC, 15 CD	Response—45.5% UC, 64.3% CD	No SAE
Muratov et al., 2006 [32]	IBD (relapse or refractory to conventional treatment)	10 (7 CD, 3 UC)	50% remission	No SAE

Author, year	Indication	No. of patients	Overall response rate	Adverse events (number or %)
Ljung et al., 2007 [33]	UC, CD, and indeterminate colitis (mostly steroid-refractory or steroid-dependent)	100	69% remission or response	15
Yamamoto et al., 2007 [34]	UC	50	52% clinical remission, 34% endoscopic remission	
Bresci et al., 2007 [35]	UC	40	70% clinical response	1
Sands et al., 2008 [36]	UC (moderate-severe)	169	17% clinical remission in GMA-group (vs 11% sham-treatment group)	—
Maiden et al., 2008 [37]	UC and CD	29	72.4% clinical remission at 6 months	55% mild and transient headache No SAE
Hanai et al., 2008 [38]	UC (moderate or severe)	70 (35 randomized to Adacolumn)	74.3% clinical remission at 12 weeks	5 mild AE 2 discontinued
Tanaka et al., 2008 [39]	UC	45	73.3% clinical remission	No SAE Transient flushing and light-headedness in few patients
Sakata et al., 2008 [40]	UC (moderate-severe)	39 randomized (17 Adacolumn, 21 Cellsorba)	76.5% clinical improvement in Adacolumn-group, 66.7% in Cellsorba-group	No SAE
de Carpi et al., 2008 [41]	Pediatric IBD	9 (5 UC, 4 CD)	55.5% remission	No SAE
Hibi et al., 2009 [42]	UC (severe, refractory to conventional medications)	697	77.3%	7.7% mild-moderate No SAE
Sakuraba et al., 2009 [43]	UC (mild-to-moderately active UC)	163	Clinical remission—54.0% in weekly GMA and 71.2% in intensive GMA	No GMA-related SAE
Cabriada et al., 2010 [44]	UC (steroid-dependent)	18 (Cellsorba—2, Adacolumn—16)	55% clinical remission (induction), 50% endoscopic remission	None
Yamamoto et al., 2010 [45]	UC (endoscopically active)	124	45% clinical remission	

Author, year	Indication	No. of patients	Overall response rate	Adverse events (number or %)
Lindberg et al., 2010 [46]	IBD (unresponsive to conventional treatment)	15 UC, 25 CD	85% clinical response, 65% complete remission	6 AE No SAE
Bresci et al., 2010 [47]	Refractory CD	16	63.3% clinical remission	No SAE
D'Ovidio et al., 2011 [48]	UC (steroid dependent/refractory)	69	58% responders	2 mild, 1 transient arrhythmia
Cabriada et al., 2012 [49]	UC (steroid-dependent)	142	41% remission at 6 months, 36% remission at 12 months	1 SAE
Yokoyama et al., 2013 [50]	UC	43	53.5% clinical remission rate	No SAE
Sacco et al., 2013 [51]	IBD	118 (83 UC, 35 CD)	71% UC clinical remission, 63% CD	
Fukuchi et al., 2014 [52]	CD	22	81.8% clinical remission at 52 weeks	No SAE
Yoshimura et al., 2015 [53]	CD (moderate-severe)	104	Remission—35.6% in weekly GMA, 35.2% in intensive GMA	22.2%
Tanida et al., 2015 [54]	Refractory UC	9	55.6% cumulative clinical remission at 10 weeks	3
Kruis et al., 2015 [55]	UC	168 (165*—68 with microscopic erosion/ulceration)	23.9% remission with GMA vs. 0% sham	
Dignass et al., 2016 [56]	UC (steroid-dependent, moderate-to-severe, with insufficient response or intolerance to immunosuppressants and/or biologics)	86	39.3% clinical remission, 56% clinical response	Majority mild-moderate
Ruuska et al., 2016 [57]	Pediatric UC	25	45% significant improvement, 25% moderate improvement	21 AE in 8/25 (32%), no SAE
Imperiali et al., 2017 [58]	UC (moderate, steroid-dependent, azathioprine-intolerant/resistant)	33	36% steroid-free clinical remission at 1 year +9% clinical response	1
Lai et al., 2017 [59]	UC	34	70.59% overall efficacy	No GMA-related SAE

Author, year	Indication	No. of patients	Overall response rate	Adverse events (number or %)
Motoya et al., 2019 [60]	UC and CD	437	46.4% clinical remission in UC, 33.3% in CD	11.4%

Overall response rate—response + remission rate.
GMA—granulocyte and monocyte/macrophage apheresis, AE—adverse events, SAE— severe adverse events, UC—ulcerative colitis.
**Number of patients included in the final analysis.*

Table 1.
Summary of studies reporting the efficacy of Adacolumn in IBD.

Author, year	Indication	No of patients	Overall response rate	Adverse events (number or %)
Kosaka et al., 1999 [61]	CD (refractory to conventional treatment)	18	50%	
Sawada et al., 1995 [62]	Both UC and CD	44 (25 UC, 19 CD)	Clinical improvement—85% in UC, 84.2% in CD	
Sawada et al., 2003 [63]	UC	39	74%	28%
Sawada et al., 2005 [64]	UC (moderate-to-severe)	25 (9 excluded; 10 randomized to active-group, 9 sham)	80% clinical improvement	1
Sawada et al., 2005 [65]	UC with toxic megacolon	6	66.7% improved, 33.3% colectomy	
Nishioka et al., 2005 [66]	UC	29 (9 LCAP, 20 cortisone)	88.9% clinical improvement, 35% remission	No major AE
Takemoto et al., 2007 [67]	UC (steroid-resistant)	71	75% initial response, 27% maintained remission >6 months	4%
Emmrich et al., 2007 [68]	UC (refractory to conventional treatment)	20	70% clinical remission	
Shimada et al., 2008 [69]	UC (moderate-to-severe)	10	80% clinical remission	None
Yokoyama et al., 2014 [70]	UC	847 (623*)	68.9% overall clinical remission, 62.5% mucosal healing	10.3% of which 0.6% severe
Kobayashi et al., 2018 [71]	UC	314	63.6% 1-year cumulative relapse-free rate, 85.1% response rate in re-treatment	

Overall response rate—response + remission rate.
AE—adverse events, SAE—severe adverse events.
**Number of patients included in the final analysis.*

Table 2.
Summary of studies reporting the efficacy of Cellsorba in IBD.

Along with the observational nature of most studies on apheresis in IBD, another important limit is that many of them were conducted in the era before biologics and novel oral therapies for IBD, when patients did not have so many options when failing steroids. While early studies evaluated the efficacy of apheresis as monotherapy in refractory IBD, more recent ones have proposed combination therapy of biologics with adsorptive apheresis, with promising results [72]. Also, recent studies have shown good results not only in induction of remission but also as maintenance therapy [73].

Not least, another limitation is that a significant proportion of studies report on small sample sizes, with very heterogeneous study groups with regard to severity and extent of disease, which limit on extrapolation of the results in all patient categories. There are some studies on special patient populations such as the elderly and pediatric/adolescent patients, in whom adverse reactions of conventional therapy can be more severe or even contraindicate their use [60].

With regard to safety, most of the adverse effects reported were mild and transient (such as fever, headache, flushing, and dizziness), very rarely severe adverse events. Despite being an invasive procedure, a study looking at the patients' perspective found that GMA is well accepted by patients suffering from IBD [74]. This is very encouraging considering that up to one in two patients encounter side effects with conventional therapies [15].

Regarding the type of anticoagulant used for the extracorporeal circulation of the blood during the apheresis session, there is one comparative study looking at nafamostat mesilate versus heparin, the latter being associated with a lower rate of AE [75].

In order to improve the outcome and safety of the procedure, some authors have also looked at the optimal apheresis treatment volume, showing that using a bodyweight adjusted volume is associated with similar therapeutic efficacy but with less AE [76].

Considering the current evidence, with the wide range of results from very heterogeneous studies, the upcoming research should focus on establishing markers to appropriately select IBD patients that would safely and cost-effective benefit from apheresis techniques [77].

Besides GMA and LCAP, novel apheresis techniques are being studied in IBD such as leucocyte/thrombocyte apheresis system, which showed promising results in a small prospective, randomized, controlled multicenter pilot study [78].

4. Conclusions

While leukocyte-derived proinflammatory cytokines have been validated as successful targets in IBD treatment, so should leukocytes themselves be considered as treatment options. As activated leukocytes migrate into the bowel wall and drive the inflammatory cascade in IBD patients, their depletion by apheresis techniques are considered beneficial to control the mucosal inflammation.

Leukapheresis, consisting in either granulomonocyte apheresis or leukocyte apheresis, are cell-based therapies with promising results in some patient categories and with a good safety profile. They have been studied as an alternative in patients with steroid toxicity, dependency or refractoriness, or in the event of contraindications to conventional therapy. Most of the early studies were not controlled, with only a few randomized controlled trials providing quality data on their efficacy. Future studies should be designed to look at selection of IBD patients who benefit most and safely from this non-pharmacological therapy.

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