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Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 72847

Manuscript Type: MINIREVIEWS

Apheresis: A cell-based therapeutic tool for the inflammatory bowel disease

Yasmin F *et al.* Apheresis in inflammatory bowel disease

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Abstract

Inflammatory Bowel Disease (IBD) is a hallmark of leukocyte infiltration, followed by the release of cytokines and interleukins. Disease progression to Ulcerative Colitis (UC) or Crohn's Disease (CD) remained largely incurable. The genetic and environmental factors disrupt enteral bacteria in the gut, which hampers the intestinal repairing capability of damaged mucosa. Commonly practiced pharmacological therapies include 5-aminosalicylic acid with corticosteroids and tumor necrosis factor (TNF)- α . New interventions such as CDP571 and TNF-blocking RDP58 report the loss of patient response. This review discusses the non-pharmacologic selective granulocyte-monocyte-apheresis (GMA) and leukocytapheresis (LCAP) that have been proposed as treatment modalities that reduce mortality. GMA, an extracorporeal vein-to-vein technique, presents a strong safety profile case for its use as a viable therapeutic option compared to GMA's conventional medication safety profile. GMA reported minimal to no side effects in the pediatric population and pregnant women. Numerous studies report the efficacious nature of GMA in UC patients, whereas data on CD patients is insufficient. Its benefits outweigh the risks and are emerging as a favored non-pharmacological treatment option.

On the contrary, LCAP uses a general extracorporeal treatment that entraps leukocytes and suppresses cytokine release. It has been deemed more efficacious than conventional drug treatments, the former causing better disease remission, and maintenance. Patients with UC/CD secondary to complications have responded well to the treatment. Side effects of the procedure have remained mild to moderate, and there is little evidence of any severe adverse event occurring in most age groups. LCAP decreases the dependence on steroids and immunosuppressive therapies for IBD. The review will discuss the role of GMA and LCAP.

Key Words: Inflammatory Bowel Disease; apheresis; granulocyte-monocyte-apheresis; leukocytapheresis; TNF- α ; Ulcerative Colitis; Crohn's Disease

Yasmin F, Najeeb H, Naeem U, Moeed A, Koritala T, Surani S. Apheresis: A cell-based therapeutic tool for the inflammatory bowel disease. *World J Clin Cases* 2022; In press

Core Tip: Granulocyte-monocyte-apheresis (GMA) and leukocytapheresis (LCAP) present as safe and viable alternatives to the conventional treatment of inflammatory bowel disease (IBD). This review summarizes the mechanism and the evidence of the efficacy of the techniques in Ulcerative Colitis (UC) and Crohn's Disease patients. The study's key findings include a commentary on special IBD patients, the unavailability of empirical evidence of reported adverse events of GMA or LCAP in the vulnerable population, such as pregnant women. It also focuses on GMA's unknown safety in UC patients and the barriers encountered in GMA or LCAP trials.

INTRODUCTION

The notion that disease-causing agents are exposed in the blood led to the widespread practice of phlebotomy and the selective removal of activated leukocytes in apheresis, which means to purify, is reflective of the former ancient therapeutic approach. Phlebotomy was utilized as a treatment for a multitude of diseases like inflammation,

fever, hypertension^[1], and extrapolating the same principle, in current times, apheresis has been studied as the potential treatment for inflammatory bowel diseases (IBD).

IBD can be termed idiopathic immune disorders characterized by intense leukocyte infiltration^[2]. Benign IBD, mediated by benign immune cells, is unyielding and continues life-long. Activated circulating leukocytes migrate to the intestine in IBD and release proinflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)- α , free radicals such as reactive oxide metabolites and nitrogen oxide. Further immune response in the region is modulated by these substances. As leukocytes get exposed to intestinal lumen antigens, there is increased activation of cells and exacerbation of tissue injury^[2]. Among the array of complications associated with IBD, the major ones include rectal bleeding, abdominal discomfort and pain, fever, anemia, weight loss, and extraintestinal complications such as arthralgia and arthritis^[3]. Ulcerative Colitis (UC) and Crohn's Disease (CD) are two major chronic, relapsing phenotypes of IBD^[2] which present with symptoms that impair function and quality of life in afflicted patients^[4]. UC is a non-transmural inflammatory disease that appears in different anatomic locations, restricted to the colon, and classified as left-sided colitis, proctitis, or pancolitis, the former two exhibiting less severe symptoms. Disease presentations include bloody diarrhea, pus, mucus passage during bowel movements^[5]. CD is a transmural inflammatory disease that can affect any section of the gastrointestinal tract from mouth to anus^[5]. The active disease is classified into the mild, moderate, and severe localized ileocecal, colonic, extensive small bowel, and oesophageal and gastroduodenal diseases^[6]. Strictures, fistulas, and abscesses can develop. At the same time, the clinical presentation is based on disease location and generally includes diarrhea, abdominal pain, fever, clinical signs of bowel obstruction, blood or mucus passage^[5]. Clinical, radiographic, endoscopic, and histological findings differentiate the two diseases. However, two serologic markers, atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) have also been immensely useful in distinguishing^[6]. The amount of neutrophils in the intestinal mucosa is quantitatively co-related with the intestinal

inflammation and probability of relapse in UC and CD^[5]. Clinical Activity Index (CAI) and Endoscopic Activity Index (EAI) are parameters for assessing UC severity, while for CD, the CD activity index (CDAI) is practiced^[6]. The CDAI score ranging from 0 to 600 allows the disease severity to be quantified over a period of seven days by assigning a weightage to each factor included. Based on the severity scores obtained, patients diagnosed with CD can be divided into three groups: asymptomatic remission (CDAI < 150), mild-to-moderate disease (150-220), and severe-fulminant disease (> 300)^[7]. Assessment of Chrons disease severity using CDAI is shown in Table 1.

The etiology of IBD remains ambiguous. However, the imbalance ²⁹ between pro-inflammatory and anti-inflammatory cytokines is strongly believed to be responsible for disease onset and progression^[8,9]. Genetic contribution is linked with disease propensity, especially among first-degree relatives^[6] and IBD development has been reported in monozygotic twins. Increased westernization of some countries paralleling IBD incidence highlights that the disease is associated with developed countries. Smoking and infection in childhood can trigger IBD, too, especially CD^[6]. A marked reduction of commensal bacteria biodiversity in IBD patients has been observed, which might have been disturbed by diet, environmental factors, or oral medications^[6]. The unbalanced relationship of the intestinal microbiota can present as UC or CD. Dysregulated immune response, coupled with disrupted enteral bacteria and genetic susceptibility, can exceed intestinal capability to repair in IBD. Owing to the complex etiology and pathogenesis, IBD has remained largely incurable. First-line treatment includes 5-aminosalicylic acid (5-ASA) or sulphasalazine, which might be used in combination with corticosteroids^[1]. Corticosteroids are mostly introduced when the condition is moderate to severe^[3]. Azathioprine is also an immunosuppressant like corticosteroid; however, both routes have a high patient predisposition to side effects^[10]. Long-term use of corticosteroids can pose a risk of developing diabetes mellitus, Cushing syndrome, osteoporosis, and vertebral fracture^[1]. Patients unresponsive to the aforementioned therapies can opt for colectomy^[1] although anti-tumor necrosis (TNF)- α

such as infliximab and adalimumab for CD and cyclosporin A (Cys A) for UC are recommended before resorting to surgical intervention^[6].

A multitude of new biologicals have been proposed that include CDP571, an immunoglobulin G4 monoclonal antibody for mild UC, RDP58 which is a p38/JNK (Janise Kinase) inhibitor known to block TNF production and inhibit IL-2, IL-12 production, and monoclonal antibodies for UC such as natalizumab^[4]. Nevertheless, drug therapies are related to adverse side effects and the inability to alter dosage and timing while the treatment is ongoing when these serious events occur^[8]. The induction and maintenance of remission *via* conventional treatments also remain questionable^[6]. In addition to these, the incidence of patient loss of response or intolerance is also reported, and these unfavorable outcomes have inspired therapies based on newer processes. Apheresis is a modality aimed at decreasing the influx of active leukocytes in the bowel, given their role as a major source of cytokines^[4]. This adsorptive removal is means by which inflammation can be blocked at an upstream level^[3]. Two different approaches for this non-pharmacological have been considered. The selective granulocyte-monocyte-apheresis (GMA) where activated granulocytes and monocytes/macrophages are selectively adsorbed, and the second one being leukocytapheresis (LCAP) which is the extracorporeal adsorption of lymphocytes, granulocytes, and monocytes^[4]. These strategies are intended to avoid the morbid events detected in the regular pharmacological courses and reduce drug toxicity, improve patient's quality of life and prevent complications and need for hospitalizations^[1].

Mechanism of granulocyte/monocyte apheresis

GMA is extracorporeal vein-to-vein apheresis. A column containing cellulose diacetate beads as GMA carriers immersed in isotonic saline within a polycarbonate casing forms the GMA device. Adacolumn is a GMA device manufactured by Japan Immunoresearch Laboratories in Takasaki^[11]. Details of structural materials made use of in the device are

outlined in Table 2. GMA was first approved in Japan in October 1999 as a safe and efficacious therapy for patients diagnosed with IBD.

Blood enters the column and exits through the column outflow, usually *via* two peripheral venous catheters. The primary mechanism of GMA revolves around the removal of inflammatory leukocytes and platelets^[12] and ultimately curbing their infiltration, evident from the composition of inflow and outflow column. Filtration of neutrophils, monocytes, and pro-inflammatory cytokines by GMA forms the basis of its implementation in patients with IBD. Making use of selective adsorption, the cellulose acetate beads adhere to Fcγ (IgG) and immune complexes (C3a and C5a)^[13], forming a link with circulating granulocytes and monocytes, with the former expressing the highest affinity for the cellulose beads.

GMA reduces leukocyte adhesion to the vessel endothelium as highlighted by an in-vitro study where two prominent vascular adhesion molecules (sICAM-1 and sVCAM-1) are usually elevated in IBD, show a marked reduction in their numbers when incubated with cellulose acetate beads at various temperatures. Even after substantial removal of phagocytic leukocytes from peripheral blood, their levels remained stable within the normal range^[12]. Aiding to the prognosis of patients with IBD, circulating blood levels of CD10-negative neutrophils increase, whereas L-selectin and inflammatory cytokines (TNF-α, IL-B, IL-8, and IL-10) are downregulated, exhibiting an overall reduction in pro-inflammatory response^[14]. Apart from reducing pro-inflammatory markers, a study revealed that GMA exhibits upregulation of CD4+, CD25+, Foxp3+, T-reg cells to normal range by the 10th week of treatment in patients with Ulcer Colitis^[14]. These T-reg cells play an essential role in maintaining peripheral tolerance, preventing autoimmune diseases, and limiting chronic inflammation^[15]. Furthermore, a study that assessed the influence of GMA on Interferon-gamma (IFN-γ) showed a marked reduction in CD4+ cells producing IFN-γ, thereby limiting macrophage activation in the periphery^[3].

The frequency of apheresis sessions depends on the nature of IBD and the time between relapse and the start of GMA therapy^[12]. Another study suggests severe UC

without corticosteroid use responds positively to a course of five sessions, whereas with severe corticosteroid refractive UC, more than five sessions are required with two to three sessions per week at the start for a better prognosis^[16].

Granulocyte/monocyte apheresis for IBD

Cure for gastrointestinal tract IBD remains elusive; however, aminosalicylates, corticosteroids, immunomodulators, and anti-TNF α inhibitors^[17] are the mainstay of treatment for IBD. Evidence for the use of corticosteroids and salicylates dates back to as early as 1990-1991 when they were first established as potent drugs for IBD^[18]. Since then, numerous studies have established them as a cornerstone of treatment for most patients diagnosed with IBD^[19-22]. Despite their efficacious nature, the safety profile of corticosteroids raises concerns as they lead to more adverse events than aminosalicylates^[23], and patients could potentially end up steroid-resistant or steroid-dependent^[24].

GMA appeared as a viable and safe option to avoid these potential adverse events associated with conventional therapy. Assessment of clinical effectiveness of GMA for IBD is performed using scores of relevant indexes. The severity of UC is classified as CAI or Rachmilewitz index^[25], whereas CDAI^[26] is equipped to diagnose clinical remission as discussed earlier. One of the earliest apheresis applications for CD in 1989 showed promising results as a statistically significant time of remission (18 mo) in the majority of patients was observed^[27].

The earliest clinical trial to test GMA as a potent treatment of UC was conducted in 2001 in Japan^[20]. Fifty-three active UC patients were enrolled in the study, receiving five sessions for five weeks using Adacolumn. This study showed notable improvement in remission by week 7, and the GMA therapy was deemed safe as only eight non-severe adverse events were recorded. Another study from Japan in 2004 compared GMA with prednisone on moderate-severe steroid-dependent active UC patients^[28]. It furthered the case of GMA as a practical option compared to steroids as patients of the GMA arm had a mean CAI score of 1.7, whereas CAI of prednisone arm was 2.5.

However, in 2008, a randomized sham-controlled trial in community-based and tertiary care centers in the US showed contrasting results^[29]. A Mayo score reduction of ≥ 3 was observed in 44% in GMA and 39% in the sham treatment group, demonstrating a non-significant difference in clinical remission and put a question mark on the efficacy of GMA in moderate to severe UC patients. The Mayo Score for UC patients, summarized in Table 3, comprises ²¹ stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment, each scored from 0-3. These doubts and concerns were put to rest by studies marking anti-TNF- α inhibitors as less effective and a 2010 meta-analysis of the effect of GMA in active UC patients^[30,31]. The meta-analysis pooling outcomes of seven randomized controlled trials (RCTs) presented a significant improvement in clinical effectiveness and remission after both 6 and 12 wk.

A 2021 meta-analysis^[32] on UC treatment with GMA comprehensively solidified the efficacious nature of GMA as compared to conventional therapy alone. The primary outcome showed GMA to induce and maintain remission in UC patients significantly (OR: 1.93, ²⁶ 95% CI: 1.28 to 2.91, $P = 0.002$); however, no significant difference was seen in adverse events. A recent open-label multicenter trial (EXPECT)^[33] paralleled these results by demonstrating a 74.4% endoscopically confirmed mucosal healing in GMA therapy patients.

As for CD, the first assessment of the therapeutic effects of GMA was carried out in 2003 in the form of a case series^[34]. Seven adult patients unresponsive to conventional medication (CM) received 5-6 GMA sessions for 5-6 wk. Five patients reaching remission saw their CDAI scores decrease from 285.4 (62) to 94.4 (3.7). Soon after, in 2004, a clinical trial of six patients unresponsive to CM saw a decrease in mean CDAI from 258.2 (36.2) to 166.5 (16.6)^[35]. In 2010, the first case reporting investigating the effects of Infliximab (IFX) in combination with GMA in a patient with CD^[36]. In the 33-year-old female, CDAI decreased from 294.2 to 83.6 by the seventh week; IFX appeared to induce and maintain remission, but GMA must be conducted side by side to maintain its efficacy.

A 2014 double-blind sham-controlled study of GMA for moderate to severe CD was published^[37]. Patients receiving GMA and sham-apheresis showed no statistical difference after nine weeks, and the effectiveness of GMA was not demonstrated. However, in 2015, a randomized trial from Japan^[38] showed remission in 16 of 45 and 19 of 54 in weekly GMA and intensive GMA, respectively. No difference in remission was observed between the two groups; however, time to remission was significantly low in the intensive GMA group without additional side effects. Ustekinumab and intensive GMA for CD was established as a safe and potent treatment option by a case report of three patients in whom clinical remission was achieved by the end of the 10th week^[39]. In 2013 prospective cohort of 35 patients of CD showed 63% clinical remission with no significant complications reported, forming an argument for GMA in patients with active CD. Moreover, a 2016 meta-analysis on GMA for IBD pooled three RCTs on CD with 362 subjects^[40]. The remission rate in CD was non-significant (OR, 1.10, 95%CI: 0.51–2.34), making use of GMA for patients with CD uncertain.

GMA treatment in special inflammatory bowel disease patients

Several studies investigate the potential use of GMA in pediatric and geriatric patients. Children diagnosed with IBD carry an increased risk of long-term complications such as colon cancer, growth and bone deformity, and micronutrient deficiencies (Vitamins B12 and D)^[41]. To curb the progression of IBD, pharmacological treatments alone are not sufficient to induce and maintain remission; thus, GMA as a non-pharmacological therapy is of greater interest in the younger population.

In 2008, a prospective pilot study investigated the outcomes of GMA in the pediatric population, enrolling nine patients with a mean age of 13 years nine months^[42]. After five sessions of apheresis, four of the five UC patients and one of four CD patients achieved remission, providing evidence of the safety and tolerability of GMA in children. Furthermore, in 2009, a retrospective study of 37 children^[43] established a significant decrease in pediatric ulcerative colitis activity index and pediatric CDAI and assisted in reducing corticosteroid intake in the patients. A recent clinical trial of 12

pediatric patients^[44] advanced the case for the use of GMA in IBD patients as 8 out of 12 patients were in clinical remission, and improvement of Mayo scores was observed in 9 patients. A 2019 multicenter retrospective study^[45] on different IBD populations enrolled a total of 437 patients. Of these 437, 125 were elderly, 53 were adolescents, and 105 patients were anemic. GMA was well tolerated in all sub-populations as 49.5% of elderly, 55.2% of pediatric, and 39% of anemic patients showed remission.

In 2005, a case report on a CD patient with Hepatitis C virus (HCV) treated with GMA was published^[46]. The authors investigated the plasma HCV levels throughout all GMA sessions and noted a 55% decrease during the five sessions. Remission of both HCV and CD were sustained in the four months of therapy. One of the major causes of concern in pregnant women is vertical transmission. A couple of studies suggested this concern as first-degree relatives and offspring are at substantial risk of getting diagnosed with IBD^[47]. A 2015 case report^[48] of a 37-year-old female consenting to the use of GMA for UC, as pharmacological treatment options could potentially put the fetus at risk, delivered the baby successfully with no side effects reported in the baby and the mother. Case reports documenting flare-ups of UC in pregnant women reported clinical remission with no adverse events seen in any of the cases^[49,50].

Safety and future of GMA

Apart from maintaining remission, the safety profile of GMA is one of its major advantages. Post-market surveillance from 53 medical institutions in Japan provides the largest ever clinical safety data; adverse events were low to mild severity^[51]. In the ART-Trial, 71.8% of the patients experienced mild side effects, whereas 7.1% underwent serious adverse events; however, none were linked to GMA. The common side effects of GMA treatment include headaches, fever, shivering, and nausea, which are easily overcome by administering medications (painkillers and antipyretics)^[52]. In the double-blind sham-controlled trial, rare instances of upper airway infections are documented^[29]. GMA is also safe for use in pediatric and pregnant patients as no

harmful impact on the fetus was reported, and the children experienced mild adverse effects only^[42,48-50].

A 2021 study examined fecal calprotectin (FC) as a valuable biomarker to track clinical remission after GMA in its early stages^[53]. It showed an 84.6% specificity when a cut-off value of change in FC was set at $< 40\%$ at one week, allowing a reduction in unnecessary invasive procedures. An 18-year-old woman with suspected Pyoderma Gangrenosum (PG), a severe UC complication, underwent ten GMA sessions combined with corticosteroid therapy. She showed drastic improvement and was discharged on the 45th day of hospitalization, demonstrating the potential use of GMA with corticosteroid treatment in cases of PG in the future^[54].

GMA presents as a viable non-pharmacological treatment option since its effectiveness in UC patients is well documented. However, large-scale RCTs and sham-controlled trials are lacking, especially in patients diagnosed with CD, making it a subject of ambiguity in such individuals. As most of the studies are conducted in Japan, there is a lack of worldwide empirical evidence on the safety and efficacy of GMA. Nevertheless, considering its high safety, GMA should be considered in specific sub-populations.

LEUKOCYTAPHERESIS

Mechanisms of leukocytapheresis

The mechanisms for LCAP rest on the understanding that during IBD, ⁵ activated leukocytes move from peripheral blood and infiltrate the mucosal tissue while attaching to specific adhesion molecules that are expressed on the endothelial surface^[55]. Immunopathology reveals that various cytokines are involved in the disease course, and as peripheral blood leukocytes are the major sources of these cytokines, these are rational targets of treatment^[4]. Leukocytapheresis was initially used ³ to treat patients ³ with chronic myelocytic leukemia and chronic lymphocytic leukemia. This was based on the principle that removal of lymphocytes producing or stimulating antibody production should eliminate the inciting agent of the disease^[4]. Leukocytes have an innate propensity to adhere to foreign bodies. The discovery that they can attach

strongly to ultrafine polyester fibers laid the basis of this method's adoption for treating patients with activated leukocyte-associated diseases^[56].

The system for leukocytapheresis was developed by Asahi Kasei Medical in Japan and was first comprehensively described by Sawada *et al*^[56]. It also functions as a direct blood perfusion device. The process initiates when whole blood is guided from the cubital or femoral vein using a pump^[57] and returned to the opposite side of the body. The column, primed with saline solution before use, has Cellsorba filled with water for injection. The contents of the column must be substituted with saline solution with an anticoagulant, mostly Nafamostat Mesylate (NM)^[57] in patients with intestinal hemorrhage or heparin as an anticoagulant^[58]. In a comparative study between these two anticoagulants, heparin was associated with a lower rate of adverse events^[59].

Leukocyte's components are removed in the cylindrical section of the column. 2-3 L of blood is processed in a single session with a flow rate of 30-50 mL/min^[55]. The column successfully removes 90%-100% of granulocytes and monocytes, 30%-60% of lymphocytes, and a lower percentage of platelets from peripheral blood^[58] and activated platelets, monocyte-platelet aggregate, and leukocyte-platelet aggregates, all of which are known sources of proinflammatory cytokines^[58]. Additionally, the leukocyte number in peripheral blood does not decrease below the normal range^[60] and baseline values of the pro-inflammatory cytokines TNF- α , IL-2, IL-8, and IFN- γ have been revealed to be near the upper limit of the normal range^[58]. Moderate LCAP is carried out once weekly for ten weeks, while intensive LCAP is performed twice weekly for five weeks. This mechanism has brought several modifications, such as using a single needle (SN), other than the conventional procedure employing a double needle (DN). SN LCAP involves one needle, one blood pump, and one valve. System of blood, vein, and pump clamping is automatically controlled as per the venous pressure and the set upper limit value of the SN control pressure. As blood is withdrawn from the patient, positive pressure accumulates in the LCAP compartment. The internal pressure of 180 mm HG is preselected, which once reached, the blood pump head stops rotating

in the venous phase, and the valve opens to return the blood to the patient until a preselected lower limit pressure of 30 mm Hg is reached^[58].

Some trials have introduced other alterations, such as one assessing LCAP in pediatric patients with UC used the EI column (Asahi Kasei Medical Co., Ltd., Tokyo, Japan) having a volume of 90 mL, which is utilized for patients with a bodyweight of 20 to 30 kg. In contrast, the EX column (Asahi Kasei Medical Co., Ltd., Tokyo, Japan) is used largely in clinical practice has a volume of 170 mL and is for patients weighing 40 kg^[61]. Another trial adjusted the patient blood volume (PBV) to 1500 mL/session for a patient weighing 50 kg and 2400 mL/session for an 80 kg patient. This contrasts with routine LCAP protocol, where the PBV is 3000 mL/session for both the 50 kg and 80 kg patients, respectively. Furthermore, a randomized controlled trial investigating UC patients administered a specific chemokine-loaded (CCL25) column to remove CCR9-expressing immunological cell populations from the circulation^[62]. A column carrying big bead streptavidin Sepharose™ matrix (average bead size 200 um) coupled with GMP manufactured biotinylated CCL25, TLA Gut was used. The objective of having a CCL25 Loaded matrix was to deplete CCR9+ cells by the affinity between the gut homing cell receptor, CCR9, and its ligand CCL25^[62].

LCAP for IBD, CD and UC

Cellsorba results in an extensive removal of white blood cell (WBC), and this reduction in WBC has been beneficial to IBD patients^[59]. Sawda *et al*^[56] also reported LCAP to be effective for IBD patients. In the initial days, the IBD Research Committee in Japan conducted a double-blind trial from 1998 to 2000, which showed statistically significant effectiveness in the LCAP group in comparison with a sham apheresis group^[56]. Several mechanisms have been proposed by which LCAP assuages IBD. The plastic lines in the apheresis column may also have an effect at the interface of the plastic surfaces and circulating leukocytes and plasma proteins IL-1, and its antagonists are pivotal in IBD inflammation and a significant decrease in IL-1 receptor antagonist (IL-1Ra) in the apheresis plastic lines during the LCAP session. In patients with active IBD, it is

ascertained that the morphologic lesions and mucosal inflammation are due to an abundance of neutrophils.²³ Pleiotropic cytokines like TNF- α , IL-1b, IL-6, IL-12, IL-23 are produced by these neutrophils with monocytes/macrophages, creating a pro-inflammatory state^[1]. Depleting the body of these leukocytes that steer the inflammatory cascade in the bowel wall can control the mucosal inflammation^[59], and is precisely what LCAP in CD AND UC is purposed for. Both CD and UC impair quality of life with severe relapses^[63], LCAP is a relatively newer approach from the conventional therapies dispensed to treat the two diseases.

In a study conducted in Turkey, six patients with CD and 20 patients with UC underwent leukocytapheresis, ten sessions for remission induction therapy, six sessions for maintenance therapy alongside the patients' associated medications. Clinical remission was observed in five of the CD patients, while 16 of the UC patients demonstrated clinical response. Notably, UC patients with extraintestinal manifestations had a drastic remission with leukocytapheresis and anti-TNF alpha therapy combination with no relapse during the follow-up duration^[63]. In 2014, leukocytapheresis was reported as successful maintenance therapy for CD. A 24-year-old male patient with long-standing CD was started on this leucocyte apheresis after being unresponsive to conventional treatments. Within a few months, the patient's symptoms and lab indices improved significantly. Patients with CD have often shown secondary loss of response with most anti-TNF agents, and given this, the apheresis treatment indicates copious potential^[64].

The response rate of leukocytapheresis has been variable in UC patients. A meta-analysis reporting efficacy of leukocytapheresis in UC patients revealed that the patients in clinical remission after 24 wk were higher in the leukocytapheresis group than the control group. The study concluded that this procedure is also more efficacious than usual therapy with continuous or intensive steroid treatment for rapid and long-term maintenance of clinical remission, stronger steroid-sparing effects, better endoscopic and pathologic improvements. In a large-scale RCT, Yokoyama *et al* indicated that LCAP is effective for treating active UC patients with moderate to severe

disease activity. Measuring through the Mayo endoscopic subscore ≤ 1 one week after treatment shows mucosal healing, an important predictive factor of long-term LCAP outcomes, 47% of patients with steroid-free UC and 33% patients with steroid-resistant UC had achieved the desired result^[65]. Of the 623 patients, clinical improvement and clinical remission were found in 73.8% and 68.9% patients, respectively^[66]. A multicentre study also determined that apheresis therapy is a viable option for enhancing the long-term prognosis of UC patients as endoscopic remission, which is highly rated as being positively associated with improved outcomes, was attained in 40% of the patient undergoing LCAP for 12 mo, higher than the control group^[67]. In a controlled randomized pilot study, alternative escalation therapy with leukocyte apheresis device was studied in mesalazine-refractory UC patients. Compared with steroid prednisolone, a similar therapeutic efficacy for induction of steroid-free remission and improvement was reported in the apheresis treatment group^[68].

The Cellsorba setup for UC treatment has been well accepted by patients. When asked about their willingness to retreat with LCAP in a hypothetical situation that their IBD relapsed, the majority answered affirmatively^[69]. A study examined the 5-year relapse-free rate in patients with moderate to severe UC and found that the 5-year relapse-free rate was higher in the ≥ 40 - than < 40 -year-old patients^[70]. Younger age was ascribed as a risk factor for early relapse after apheresis therapy which might be a better therapeutic option for maintenance of remission in UC patients aged ≥ 40 years^[70]. Moreover, Kobayashi *et al* conducted a retrospective observational study to evaluate the clinical outcome at one year and identified risk factors for relapse of UC after LCAP. 3- and 6-mo remission rates were 88.6% and 79.3%, respectively, and the significant risk factor identified for relapse was a high leukocyte count after LCAP^[71].

LCAP for special IBD patients

Steroid-resistant or steroid-dependent UC patients respond well to apheresis and can be considered as an effective adjunctive therapy for these patients^[3]. Comprehensive data from uncontrolled studies also show a high response rate in corticosteroid-naïve

patients and a remission rate of approximately 50% in patients with steroid-dependent or steroid-refractory UC who received apheresis treatment^[72]. A 27-year-old patient from Croatia had a relapse of UC secondary to anemia and side effects to a previously prescribed steroid therapy and an inadequate response to azathioprine. The patient was started on LCAP, and after 12 sessions, a good clinical response was achieved and a clinical remission within two years of treatment^[73]. In a pilot study assessing steroid-resistant active UC patients undergoing centrifugal leukocyte apheresis, the severity score dramatically decreased, and clinical symptoms such as abdominal pain, tenderness, and haematochezia improved with a reduction in inflammation, improvement in oedematous change, and cessation of bleeding in colonic mucosa within four weeks in 92.9% of the patients^[74].

Toxic megacolon is a fatal complication of UC, CD, and other IBD. In a small-scale clinical trial enrolling patients with fulminant or severe UC with TM were treated with LCAP. In four of the six patients, remission was attained, with “excellent improvement” established by both clinical and endoscopic parameters. In a patient with aortitis syndrome coupled with UC, LCAP treatment weekly for seven weeks mitigated the exacerbating of the two complications^[3]. Itou *et al* report a case of a male patient with UC and Primary Sclerosing Cholangitis (PSC) who received LCAP once a week for five weekly sessions. A noticeable improvement in clinical symptoms and colonoscopic findings of UC was observed with decreased serum levels of ALP, total bile acids, and total bile salts, while there was no aggravation of either UC or PSC till 1-year follow-up^[75]. Terai *et al* reported a case of a 41-year-old male patient with total colitis type UC complicated with Sweet’s Syndrome. The patient underwent treatment with 40 mg/day prednisolone and leukocytapheresis, and within four weeks, skin eruption completely disappeared, and clinical features of UC and laboratory parameters also subsided^[76]. In a retrospective analysis, Shibuya *et al*^[77] studied UC patients who had received LCAP and included the elderly, patients on steroids, biologics, a calcineurin inhibitor, and with extra-intestinal complications. Clinical remission rates were 36.4% in the elderly, 54.2% in the non-elderly, regular UC patients (without extra-intestinal complications).

In UC patients with extra-intestinal complications, 84.6% had an effective rate of therapy. These complications included nodular erythema, pyoderma erythematosus, systemic lupus erythematosus, skin ulcers, and arthralgia. In a multicenter, prospective study involving steroid-refractory UC pediatric patients, clinical remission was observed in 83% of the patients in response to LCAP, which was similar to an efficacy exhibited in adults^[61].

Safety of LCAP

Leukocytapheresis, is an effective and safe natural biologic therapy reducing inflammatory cytokine release and displaying drug-sparing effects, reducing the number of patients undergoing colectomy or developing or getting exposed to powerful immunosuppressants^[4]. As demonstrated in a study where LCAP was performed in CD and UC patients, the procedure was well tolerated and deemed safe in the patients^[59] and most side effects reported were mild and temporary and with no severe adverse events (AE) reported.

In UC patients receiving LCAP, side effects occur during 2.3% of apheresis sessions. The most frequent ones are headaches occurring in 1.58% of cases, fever/chills in 1.29%, 1% have anemia, while elevated AST/ALT and nausea are experienced by 1% and 0.8% of patients, respectively^[78]. In an RCT, Naganuma *et al* reported an 11.3% rate of adverse events in the UC group receiving apheresis therapy. Most AEs were linked with anticoagulants and were reversible. Over one year of surveillance showed an absence of severe AE^[67]. A cohort study validated the safety and efficacy of the procedure for elderly patients with the non-appearance of any serious AE and a remission rate of almost 90%^[67]. Nishoka *et al* conducted a study with steroid naïve UC patients who started on Cellsorba leukocytapheresis. In comparison with the steroid group, the LCAP patients had a lower rate of severe AE^[79]. These findings corroborate data from multiple large-scale trials, which concluded that adverse effects occur less in LCAP than in steroid therapy^[73].

Post-hoc observational study analysis of steroid-free UC patients had an overall incidence of AEs as 10.3%, which were generally moderate, and patients recovered or

significantly improved from them. Specifically, in the elderly group, there were no severe infection or thrombosis cases^[80]. A study constituting pediatric patients who had UC and were resistant to steroids reported AEs in 61% of the participants. Those included a decrease in hematocrit, pain at the infusion site, and a decrease in red blood cell count. None of them were serious, and treatment continued as predefined^[81].

Pressure fluctuations in the Cellsorba column account for some of the adverse events observed. An increase in ultrafilter pressure that occurs due to a pressure difference between the inlet and outlet chambers of the LCAP is a cause of concern. A study attempted a Body Weight Adjusted LCAP (BWA-LCAP), which had few variations from the routine LCAP. Reducing the processed blood volume (PBV) after effectively employing the BWA-LCAP procedure can minimize this AE that can cause micro thrombosis^[74]. Additionally, UC patients present with symptoms of watery diarrhea and bloody stool, becoming hypovolemic. It is necessary to carefully monitor the procedure and ensure sufficient blood flow during the session^[82]. A transient lymphopenia is also observed during Cellsorba leukocytapheresis and could stimulate autoimmunity and render limitations in the treatment^[58].

Nagase *et al*^[69] studied IBD, and in their patient population, with 4.5% reported AE while no AE was reported in the CD group specifically. Symptoms of palpitations, itching sensation on the face, and discomfort were reported. However, these did not required any medication. When assessing IBD patients that included diagnosed cases of UC and CD, moderate reactions were encountered, with most patients recovering after the first clinical treatment. Severe reactions were less experienced when heparin was used as the anticoagulant than NM^[83]. When Shibuya *et al*^[77] examined the effectiveness of cytapheresis in elderly and non-elderly patients, an episode of allergic reaction to NM occurred in one 47-year-old patient, which too abated after a few hours. Despite being an invasive procedure, studies have elucidated that LCAP is well tolerated by most age groups, can be a relatively safe and therapeutic option, especially in patients who have had prior AE and have qualms about immunosuppressive cures^[82].

Future of LCAP

IBD is a manifestation of unrestrained immune activity, initiated and maintained by inflammatory ¹⁴cytokines including TNF- α , IL-1 β , IL-6, IL-12. Due to the poorly understood etiology of the disease, drug therapy has mostly been empirical and aimed at targeting inflammatory mediators, while the conventional medications have not been potent enough to resolve the illness^[4]. When the drug response is poor, leukocytapheresis is an important adjunct for treating IBD. While precise mechanisms are elusive, LCAP can reduce specific cell populations^[58]. The procedure is straightforward, widely accepted by patients, and has minimal toxicity, making it a plausible option. Not only are leukocytes entrapped, but IFN- γ is suppressed as well, which can indicate a sustained, long-term response to the procedure^[3].

For understanding the long-standing effect of the treatment, it is imperative to delineate the processes of IBD as it would aid in the careful selection of patients for LCAP^[58] who can effectively and safely maximize its use^[59]. Wide-ranging studies have been conducted for LCAP, and in the context of the results obtained, specific markers should be established for screening patients for undergoing apheresis^[58]. The Lemann score is one such technique, which is a scoring system for CD and can ¹be used to gauge the effect of medical therapies on the development of bowel damage. This instrument facilitates the identification of patients with severe epithelial and bowel damage^[6]. Patients with extensive ulcers and UC that are refractory to drugs are not recommended LCAP therapy. Thus, baseline features help identify patients who are likely to respond to apheresis, thereby preventing unprofitable use of the approach^[58].

LCAP has been received well, especially for steroids sparing effect and even attaining remission from the disease earlier than conventional treatments^[59]. Certain changes, such as the SN LCAP, which has diminished the time to start apheresis, are found to have reduced the burden on the UC patients. LCAP has proven to be successful in inducing and sustaining remission in chronic active UC patients^[72], however, there is still some inadequacy in clarification of the mid-and long-term prognosis of patients

treated. Some research has proposed 5-ASA biologics as maintenance therapy after apheresis, while thiopurine has also been suggested. It is vital to discern the most appropriate maintenance route as the need arises in patients at risk for AE after initiation of remission after apheresis^[67].

LCAP is still a rare modality, and large-scale studies are warranted to explore its long-term benefits. The procedure is expensive, especially in contrast to other extracorporeal methods adopted for treating UC^[73]. However, the cost, alongside the continuous venous access, is discussed as a potential barrier to LCAP's use as a long-lasting respite from the disease. Using scales such as the Inflammatory Bowel Disease Questionnaire^[73], quality life can be applied to judge patient preference, which would be a leading factor in determining LCAP use in the future. The optimal frequency of treatments, parallel comparisons with IBD drugs needs to be evaluated thoroughly to further ascertain LCAP's usage.

CONCLUSION

IBD results from an imbalance between anti-inflammatory and pro-inflammatory cytokines from over-activated leukocytes. Pharmacological treatment options for IBD have produced unsatisfactory outcomes, which risk long-term side effects. Therefore, apheresis, GMA or LCAP, are being considered viable options to deplete the leukocyte population. Available literature suggests GMA be safe in UC patients. However, its efficacy and safety are undocumented in CD patients. Similarly, the lack of empirical evidence about LCAP's long-term benefits is primarily due to low cost-effectiveness. These mandates large randomized clinical trials in IBD patients of different age groups, along with a cost-benefit analysis of the procedure.

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