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CONCISE REVIEW

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Adsorptive cytapheresis in ulcerative colitis: A non-pharmacological therapeutic approach revisited

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Abstract

Adsorptive cytapheresis proves effective in a proportion of patients affected by ulcerative colitis. Relatively high cost and the need for apheresis facilities, prevented the widespread use of this therapeutic approach. More so following the introduction of anti-TNFα biosimilars which proved both effective and inexpensive. Anti-TNFα agents, however, are burdened by high rate of primary and secondary non-response and prompt switching to new, high-cost biologics, and small molecules. The present review analyzes advantages and disadvantages of adsorptive cytapheresis in the present clinical scenario and suggests its repositioning in the therapeutic workup of selected subgroups of ulcerative colitis patients. The extremely favorable safety profile makes adsorptive cytapheresis a viable therapeutic option in elderly and high-risk UC patients, as well as potential second-line treatment in corticosteroid-dependent patients and poor responders to first-line biologics.

KEYWORDS

adsorptive cytapheresis, efficacy, inflammatory bowel diseases, mechanisms of action, safety, side effects, ulcerative colitis

1 | INTRODUCTION

Therapy of ulcerative colitis (UC) is primarily based upon the combination of the traditional drugs, including steroids, mesalazine and immunomodulators, and biologics. The availability of anti-TNFα agents at the end of last century represented a therapeutic breakthrough, and biosimilars reduced costs which are the main setback of new therapies.[1] Efficacy associated to acceptable cost rendered less appealing alternative approaches, adsorptive cytapheresis (AC) included. This non-pharmacological procedure carried out to remove selected cell populations from peripheral blood proved effective in a proportion of inflammatory bowel disease (IBD) patients.[2,3] Primarily used in Japan, where is considered a first-line therapeutic option in moderate UC, it has also been licensed in the European Union for IBD and chronic inflammatory skin diseases, such as pustular psoriasis. Nonetheless, AC has never been widely accepted in Western Countries because of relatively high costs, the need for cooperation with apheresis centers, and conflicting data on its real efficacy.

High rate of primary and secondary loss of response of anti-TNFα agents, and the introduction of high-cost biologics or small molecules as second-line therapy, modified

the clinical scenario. Economic considerations, associated with the extremely favorable safety profile of AC, also in pediatric and elderly patients, prompt reconsidering strategies, at least in selected subgroups of UC patients.

2 | EFFICACY OF BIOLOGIC DRUGS, LOSS OF RESPONSE, AND ADVERSE EVENTS

The efficacy of biologics in attaining clinical response and remission, steroid-free remission, and mucosal healing is well documented for anti-TNFα agents, immune cell trafficking inhibitors,[4] anti-IL 12-23,[5] Jak inhibitors,[6] and other small molecules. However, the number of patients required to obtain an additional remission using different biologics compared with placebo (NNT) varies from 3 to 14 patients.[7] Including the placebo effect figures are about halved, indicating that biologics' efficacy is far from optimal, more so considering deep remission as the primary therapeutic endpoint.

Even in responders, the most widely used biologics, anti-TNFα, show 10% to 20% yearly secondary loss of response, partly related to the production of antibodies.[8,9] This in turn, leads to low trough levels of the drug, requiring dose adjustment to prevent loss of response.[10,11] Seven to 65% patients stop the index therapy within the first year.[12] Thus, the probability of at least one switch to different biologics is high, reaching 26% in the first year, with an additional 15% in the following 12 months.[13] New biologics and small molecules, in turn, besides being more expensive than anti-TNFα, are burdened by comparable rates of primary and secondary loss of response.

Moreover, biologics are associated with the occurrence of adverse events (AE), that in some instances are severe, and life-threatening. An increased risk of hepatosplenic lymphoma and melanoma has been reported following anti-TNFα agents, although largely resulting from combination therapy with immunomodulators,[14] and severe infections, TBC included.[15] Anti-TNFα agents are thus considered unsuitable for elderly patients, and those with severe comorbidities or increased infective risk, despite the need for effective therapy for active UC. AC may thus represent a viable alternative to first-line therapeutic strategies.

3 | MECHANISMS OF ACTION OF ADSORPTIVE CYTAPHERESIS

Adsorptive cytapheresis is a non-pharmacological procedure that removes selected cell populations from peripheral blood, using different extracorporeal apheresis techniques.

The extracorporeal, vein-to-vein apheresis system used in AC consists of blood circuit lines, a blood pump controlling flow-rate and duration of the procedure, a disposable single-use column, and a monitoring control system. During the procedure, blood enters in- and flows out the column through two distinct venous catheters placed in the cubital or femoral vein. In some centers, a single-needle, single-catheter technique, involving the use of a pump equipped with a valve controlling the direction of blood flow has been used.[16] The procedure is usually performed on a weekly basis, but more aggressive, twice-a-week strategies have been proposed to foster efficacy.[17,18]

The most widely used type of AC is granulocyte-monocyte apheresis GMA (AdacolumnTM, JIMRO, Takasaki, Japan) using columns containing 220 g cellulose diacetate beads in 130 mL of isotonic sterile saline solution, while leucocytapheresis (LCAP) (Cellsorba, Asahi Kasei Kuraray Medical, Tokyo, Japan) using non-woven polyester fiber filters, has been mainly utilized in the past.

GMA selectively adsorbs activated granulocytes, and monocytes expressing Fcγ, C3a, and C5a immune complexes.[19] The standard 1 hour, 30 mL/min GMA session filters 1800 mL blood, and adsorbs 25% activated granulocytes and 20% monocytes, 2% to 7% lymphocytes and virtually no erythrocytes.[20]

The standard LCAP session uses higher blood flow rates (50 mL/min) compared with GMA, thus filtering more blood. It removes 90% granulocytes, 79% monocytes, over 55% platelets as well as an average of 50% lymphocytes.[21,22]

A third, more recent, and less widely used technique, Immunopure utilizes polyarylate resin bead columns and a flow-rate of 30 mL/min, in 1-hour sessions. The effect of this AC is intermediate between GMA and LCAP, adsorbing 35% granulocytes, 45% monocytes, 45% platelets, and 3% lymphocytes.[22,23]

The removal of activated granulocyte, lymphocytes monocytes, and aggregated platelets by all types of AC results in downregulation of proinflammatory cytokines, IL8 included, and IFNγ, as well as upregulation of CD4+, CD25+, Foxp3+ T-reg cells, lessening acute, and chronic inflammatory processes.[24-27] The reduction of L-selectin and other cell adhesion molecules following AC, affects chemotaxis and migration of granulocytes, monocytes, and leucocytes into the inflamed gut.[28,29]

4 | EFFICACY OF ADSORPTIVE CYTAPHERESIS IN ULCERATIVE COLITIS

Several open/ retrospective studies documented the efficacy of AC in improving clinical scores and endoscopic findings in UC, with response rates ranging from 60% to 80%

TABLE 1 Efficacy of adsorptive cytapheresis in adult patients.

Author	Number of patients	Type of AC	Control therapy (CT)	Efficacy of AC	Efficacy of CT	Follow-up
Hanai 2004[25]	69	Frequency: 1/week (if CAI < 12) or 2/week in the first 3 weeks then 1/week (if CAI > 12) Duration: up to 10 weeks	Prednisolone (30 vs 12 mg/day/patient)	83% (CAI < 4)	65% (CAI < 4)	24 weeks
Bresci 2007[26]	40	GMA Frequency: 1/week Duration: 5 weeks[a]	Methylprednisolone 0.8-1 mg/kg/day for 2 weeks, tapering 4-6 mg/week	70% (CAI < 6)	60% (CAI < 6)	12 weeks
Hanai 2008[27]	70	GMA Frequency: 2/week for 3 weeks, then 1/week Duration: up to 8 weeks[a]	Prednisolone, 40-60 mg/day for 5-10 days	74.3% (CAI ≤ 4)	48.6% (CAI ≤ 4)	12 weeks
Sands 2008[28]	215	GMA Frequency: about 1/week Duration: 9 weeks	Unchanged medical therapy	44% (Mayo score reduction >3)	39% (Mayo score reduction >3)	12 weeks
Domenech 2018[29]	123	GMA Frequency: about 1/week Duration: 7 weeks	Prednisone 40 mg/day (vs GMA plus prednisolone at the same dosage)	45% (Mayo score reduction >3)	24% (Mayo score reduction >3)	12 weeks
Dignass 2018[30]	95	GMA Frequency: 1/week Duration: 5-10 weeks	Mean prednisone 13.5 mg/day (steroid vs GMA plus steroid)	53.2% (CAI ≤ 4)	43.3% (CAI ≤ 4)	12 weeks
Fukuchi 2022[31]	78	GMA Frequency: 2/week Duration: 5 weeks	—	43.6% relapses (CAI score >7 points)	—	156 weeks

Abbreviations: AC, adsorptive cytapheresis; CAI, clinical activity index; CT, control therapy; GMA, granulocyte/monocyte apheresis.
[a]5-ASA treatment was permitted in both groups.

(Table 1).[17,30-35] Data were summarized in a large metanalysis reporting data from 594 patients, from seven trials.[2]

Objective difficulties and ethical considerations limited the number of randomized, sham-controlled, double-blind studies. A significantly favorable outcome (80% vs 33% placebo) was reported with LCAP,[36] but not with GMA (remission 17% vs 11% placebo, response rate 44% vs 39%).[33] The discrepancy is unclear. It likely reflects methodological biases in Sands' study,[33] which included patients with minimal histological inflammation, more than different efficacy of LCAP and GMA.

Two randomized studies investigated the efficacy of GMA in steroid-dependent patients. A prospective multicentric European study evaluated the advantage provided by GMA during tapering, in steroid-dependent UC patients.[34] Steroid-free clinical- and endoscopic remission at week 24 was non-significantly better in the GMA group vs tapering alone (13% vs 7%, respectively). The efficacy of GMA was also investigated in a multicenter controlled trial in a group of patients with aggressive moderate-severe UC.[35] Immunomodulators and TNFα agents, as single therapy or in combination had proven ineffective in this series of steroid-dependent/resistant patients. GMA led to remission in onethird of patients at week 24 and 48, and steroid-free remission in onefourth of patients. Sustained remission at 1 year was observed in 27.7% of patients.

GMA was used in alternative to corticosteroids in a series of patients with mild-to-moderate UC, leading to clinical improvement in 58.2%.[37] Moreover, intensive, twice-a-week GMA, proved more effective than the standard once-a-week schedule, in inducing mucosal healing and long-term maintenance of remission in the absence of steroids.[17] Reducing the interval between sessions worked again in case of relapse.[18] These data support the conclusion of a previous meta-analysis reporting that GMA is superior to corticosteroids in inducing clinical

TABLE 2 Efficacy of adsorptive cytapheresis in addition to biologics in adult patients.

Author	Number of Patients	Type of AC	Biologic therapy	Efficacy of AC alone	Efficacy of AC and biologics	Follow-up
Song 2021[35]	60	GMA Frequency: n.r. Duration: n.r.	Adalimumab	43.33% (partial Mayo score ≤2)	63.33% (partial Mayo score ≤2)	—
Tanida 2021[36]	4	GMA Frequency: n.r. Duration: n.r.	Ustekinumab	—	50.0% (partial Mayo score ≤2)	10 weeks
Yokoyama 2020[37]	14 (7 UC)	GMA Frequency: 1/week Duration: 5 weeks	LOR to Infliximab	—	64.28% (partial Mayo score ≤2)	24 weeks
Rodriguez-Lago 2019[38]	47	GMA Frequency: 1-2/week Duration: 5-10 weeks	PNR or LOR to anti-TNFα	—	32% (partial Mayo score ≤2)	24 weeks
Rodriguez-Lago 2019[39]	8	GMA Frequency: 1-2/week Duration: 2–17 weeks	PNR or LOR to Vedolizumab	—	38% (partial Mayo score ≤2)	30 weeks

Abbreviations: AC, adsorptive cytapheresis; CAI, clinical activity index; GMA, granulocyte/monocyte apheresis; LOR, loss of response; PNR, primary non-response; PUCAI, pediatric ulcerative colitis activity index; UC, ulcerative colitis.

remission (OR 2.23).[38] The meta-analysis included studies carried out in Japan and western countries, but did not take into consideration the body weight of patients. Considering that in western countries the mean body weight is higher than in Japan, increasing the volume of treated blood may increase the efficacy of GMA, as documented in LCAP-treated patients.[39]

Interestingly, adsorptive cytapheresis induces clinical remission and response, and steroid-free remission in about 40% of patients showing insufficient- or loss of response to biologics (Table 2).[40-44] The association of GMA to the anti-TNFα adalimumab increased the remission rate from 42% to 63%.[40] Following secondary loss of response to infliximab the combination therapy with AC reduced the circulating levels of anti-infliximab antibodies, increased the trough levels of the drug, and restored clinical effectiveness in twothirds of patients, even in the absence of dose optimization.[42] The association of ustekinumab with GMA proved effective in few patients with refractory UC.[41] Some evidence suggests the efficacy of GMA in association with the anti α4 β7 integrin vedolizumab following loss of response to the drug.[44,45] This could be anticipated, considering the reduced migration of leucocytes in the inflamed areas resulting from adsorptive cytapheresis. The response to GMA in relation to the use of immunomodulators (IM) or biologics has been recently summarized by Iitzuka,[46] showing that previous exposure to biologics, but not to IM, reduces the efficacy of AC from 44.2% to 29.4%. These results are nonetheless good, considering that AC was used as second- or third-line therapy in a particularly problematic subset of patients.

Response rate, clinical remission, and mucosal healing rates in elderly patients are like those reported in adults, but delayed onset of efficacy is not rare (Table 3).[47-49] Efficacy of AC has been reported in small series of pediatric patients (Table 3).[48,50,51] Pregnancy does not represent a contraindication to adsorptive cytapheresis[48,52,53] and, again, the response rate is good.

5 | SAFETY AND ADVERSE EFFECTS OF ADSORPTIVE CYTAPHERESIS

The main strength of AC resides in its excellent safety profile. Only few serious AE have been so far observed in GMA and LCAP.[54-57] Occasional cases of severe infection and one of spontaneous abortion have also been reported.[34,58] Worsening of UC, which by definition has been included among AEs, more likely represents a therapeutic failure, than a consequence of apheresis.[59]

The prevalence of mild to moderate AE varies in different series from 2% to 95%, reflecting the attitude of different authors.[33,60] AE were almost invariably mild, usually subsided reducing the blood flow rate and resulted in stopping the apheresis session in <2% of procedures. It can be speculated that in some instances minimal AE was considered irrelevant and not reported, thus contributing to the widely differing prevalence of AE in the literature. Indeed, further apheresis sessions were not prevented by the occurrence of AE, nor was affected the overall response rate (48% vs 47% in those nonpresenting with AE).[54] Finally, a proportion of AE was related to the anticoagulants heparin and nafamostat mesylate (8% of patients).[61] Blood access and feasibility problems accounted for AE in an additional 2% of procedures.[62]

Transient headache was the most frequent mild AE, occurring in 10% to 33% of patients and 4% to 14% of procedures. Nausea, fatigue, lightheadedness, and mild hypotension were also reported in some, but not all series,

TABLE 3 Efficacy of adsorptive cytapheresis in elderly and pediatric patients.

Author	Population	Number of Patients	Type of AC	Efficacy of AC	Follow-up
Komoto 2018[42]	Elderly patients (age <65 years)	65	GMA Frequency: 1/week Duration: 5-10 weeks	78.5% (CAI ≤ 4)	2 weeks after the last session
Motoya 2019[43]	Elderly patients (age <65 years)	118	GMA Frequency: 1 or more/week Duration: Up to 10 sessions	49.5% (Partial Mayo score ≤2)	—
Shibuya 2019[44]	Elderly patients (age <65 years)	11	GMA Frequency: 1-3/week Duration: Up to 10 sessions	72.7% (CAI ≤ 4)	4 weeks after the last session
Motoya 2019[43]	Pediatric patients (age ≤18 years)	40	GMA Frequency: 1 or more/week Duration: Up to 10 sessions	55.2% (Partial Mayo score ≤2)	—
Ruuska 2016[45]	Pediatric patients (age ≤18 year)	25	GMA Frequency: 1/week Duration: 5 weeks (plus up to 3 further sessions, based on clinical response)	45% (PUCAI decrease of ≥35)	12 weeks
Rolandsdotter 2018[46]	Pediatric patients (age ≤18 years)	12	GMA Frequency: 2/week Duration: 5 weeks	60% (PUCAI <10)	Median follow-up of 93 days

Abbreviations: AC, adsorptive cytapheresis; CAI, clinical activity index; CT, control therapy; GMA, granulocyte/monocyte apheresis; PUCAI, pediatric ulcerative colitis activity index.

during or immediately following AC, in up to onefourth of patients, and <5% of procedures.[33,54,60,62,63] Transient lymphopenia was observed in few patients treated with LCAP.[16]

Overall, the safety profile of AC proved better than that of any other drug used for treating UC patients, including steroids, immunomodulators, and biologics.[2,46,62,64,65]

Association of AC with biological therapy increased the response rate, but not AE.[41,43-46,64,66]

The overall occurrence of AE in elderly patients is slightly higher than that of adults (OR 1.3, CI 0.61-2.79).[48] As the prevalence of mild and moderate AE is comparable to that observed in younger age groups, the observed difference is due to 5% occurrence of serious AE, largely related to pre-existing comorbidities.[47,48,57,67,68]

GMA and LCAP are safe in pediatric patients, but technical difficulties, consisting in blood access problems or pain at the infusion site, more often occur in children than in adults.[50,51,69] Transient headaches and nausea have occasionally been reported in children and the few pregnant women treated with AC.[52,53,68,70]

Thus, available evidence indicates that the occurrence of clinically relevant AE is extremely low, and the procedure can be considered safe in all age groups as well as in patients with concomitant comorbidities.

6 | CONCLUSIONS

Apheresis in UC patients has so far been used in few tertiary referral centers, outside Japan, and a relatively small number of patients. The need for coexisting apheresis facilities, relatively high costs compared with anti-TNFα biosimilars, as well as doubts concerning clinical efficacy, all limited the utilization of AC. Indeed, few sham-controlled, double-blind studies were carried out, with non-univocal results.[33,36] The issue has been previously discussed. However, a number of non-blinded trials, and post-marketing surveys carried out in large series of patients, suggest that clinical, endoscopic, and histologic improvement, mucosal healing included, are comparable to that of steroids, immunomodulators and biologics.[2,17,62,71] Short duration of disease and steroid naïve condition, as expected, are the best predictors of response to AC.[19,57,72] This is true for any other UC therapy. All considered, cytapheresis cannot be proposed as first-line therapeutic approach in the majority of patients. Conversely, successful steroid tapering in steroid-dependent patients[30] and the capacity to restore clinical response after secondary loss of response to anti-TNFα agents even in the absence of dose escalation[40,42,43] represent potential useful applications of AC.

Economic issues, which prevented in the past widespread use of AC must be reconsidered in comparison to high-cost, new-generation biologics. The switch to these drugs following primary or secondary failure of anti-TNFα agents should be weighed against adding up AC to the ongoing therapy, in the absence of dose escalation. The same applies to anti-lymphocyte trafficking agents, in which the mechanisms of action of AC result in enhanced therapeutic efficacy.[44,45,73,74] A 30% response rate in case of failure to first- or second-line biologics has been reported

following AC. Similar figures have been reported in patients switched to more expensive, new-generation biologic agents. Thus, re-evaluating the economic burden of differing therapeutic strategies is crucial, more so considering that optimization or dose-escalation has been proposed for new, costly molecules in patients with inadequate response or loss of response to standard doses.[74]

Another mainstay of apheresis is the extremely favorable safety profile, making AC a valuable alternative in high-risk, and elderly patients. The same likely applies whenever concomitant Cytomegalovirus infection contraindicates other therapies or increases the risk of serious AE.[75]

The therapeutic scenario of UC is rapidly changing, as many new, high-cost biological agents are in the pipeline and shall be available in the next future. They include new anti-IL-23 agents and selective JAK inhibitors, S1P receptor agonists, and TLR9 agonist. More options imply more difficult decision making. Critical analysis of specific patient's conditions, risk factors, and accurate cost/effectiveness and cost/risk evaluation of different therapeutic agents will help in optimizing individualized treatment. The positioning of cytapheresis in the therapeutic workup of UC patients should thus be re-evaluated on the base of efficacy, safety, and costs which are higher than those of traditional drugs and anti-TNFs, but comparable to those of new biologics and small molecules. The ASFA guidelines stated that UC represents a Category II, Grade 1B indication for adsorptive cytapheresis,[76] but the opinion is not largely shared by gastroenterologists.[77] New real-life data, and rapidly changing scenarios suggest that adsorptive cytapheresis represents a valuable second-line therapy in selected subgroups of UC patients, including poor responders to first-line biologics, as well as cortisone dependent-, high-risk- or elderly patients.

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The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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