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Current view

Current status on the clinical usefulness of apheresis in patients with inflammatory bowel disease

J.K. Triantafillidis, P. Cherakakis

SUMMARY

In this review the current aspects concerning the application of leukocytapheresis in patients with inflammatory bowel disease are briefly discussed. Leukocytapheresis has already been applied in patients suffering mainly from diseases affecting the immunological balance. The procedure has recently been tried in patients with ulcerative colitis and Crohn's disease as well, with promising results. Leukocytapheresis is gaining in interest as a therapeutic procedure of the near future, because it removes - in a short time- a number of immunologically active cells, which are well known to actively participate in the inflammatory cascade, leading to tissue damage. However, further studies are needed in order to better clarify the role of leukocytapheresis in the maintenance treatment of patients with inflammatory bowel disease, either alone, or in combination with drugs of known efficacy in IBD.

Key words: Apheresis, Leucocytapheresis, Inflammatory bowel disease, Ulcerative colitis, Crohn's disease

INTRODUCTION

Efforts to remove plasma and/or various cells from the circulation of patients with inflammatory bowel disease, can be recorded back to 1989.[1] During the last 10 years efforts aiming to introduce this kind of treatment in patients with inflammatory bowel disease were successful only in Japan, whilst little work has been done in USA and Europe.[2-10]

This kind of treatment, termed apheresis, has been investigated in several diseases such as rheumatoid arthritis, ophthalmic Grave's disease, Behcet's disease, pemphigus vulgaris, systemic lupus erythematosus, renal disorders, multiple sclerosis, acute leukemia, and inflammatory bowel disease.[11,12] It seems, however, that today a new era has arrived concerning the application of leukocytapheresis in inflammatory bowel disease, because of the tremendous progress achieved in the field of pathophysiology of IBD and the understanding of the role of immunocytes and their products in the initiation and perpetuation of inflammation in the intestinal wall.

Technique

Two methods of removal of leukocytes from the circulation have been reported. The first uses extracorporeal circulation (on-line system) and the second leukocyte elimination filters for blood transfusion to leukocytapheresis without the use of extracorporeal circulation (off-line leukocytapheresis system). The latter method was applied by Endo et al[4] who collected each time 400 ml of peripheral blood and re-infused it through a leukocyte elimination filter once weekly for 5 weeks. The extracorporeal device that has been developed for selective adsorption of granulocytes, and monocytes/ macrophages from peripheral blood of patients with ulcerative colitis contains a column, which is filled with carriers (G-1 beads) of 2mm diameter, made from cellulose diacetate.[10] According to Sawada et al[3] whole blood is pumped out from 1 cubital vein at a 50 ml/min flow rate with a Plasauto 1000 apheresis unit. (Asahi Medical Co., Ltd, Tokyo, Japan). Mafamostat mesilate anticoagulant is added to it. Then the anticoagulant whole blood is passed through a leukocyte removal filter (Cellsorba, Asahi Medical Co. Ltd., Tokyo, Japan), and the treated blood returns to the patient. Three thousand milliliters

Department of Gastroenterology, Saint Panteleimon General State Hospital, Nikea, Greece

Author for correspondence:

John K. Triantafyllidis, MD, 8 Kerasountos str., 124 61 Haidari, Athens, Greece, Tel.: 210-5819481, Fax: 210-5810970, e-mail: jkt@panafonet.gr

of whole blood is processed during each session. Therapy is usually performed once weekly for 5 weeks as acute treatment and then every 2 to 6 weeks as on-going maintenance therapy.

The removal of leukocyte components has also been achieved by the centrifugal method, using fiber technology or column technology, leukocyte components can be removed simply. The latter methods could be regarded as more effective compared to the centrifugal method in removing numbers of cells. However, it must be stressed that each type of leukocytapheresis removes different kind of cells. It is obvious that if, theoretically, we know what kinds of cells must be removed, then we can select the best method for removing the responsible cells.

Sawada et al[6] proposed that the centrifugal method must be called lymphocytapheresis, because it selectively removes 40% of neutrophils and more than 60% of lymphocytes. The cellulose beads in a G-1 granulocyte removal column method removes only granulocytes and monocytes but no lymphocytes, and therefore could be called granulocytapheresis. Finally the procedure in which the Cellsorba leukocyte removal filter is used, must be called leukocytapheresis, because 99% of both granulocytes and monocytes and about 70% of lymphocytes are removed.

Recently, a non-woven polyester fiber filter has been used. Using this technique, Kawamura et al,[13] were able to remove 30-70% of leukocytes and 30-68% of their subsets.

Pathophysiology

The effective mechanism of cytapheresis for inflammatory bowel disease is controversial. However, the removal of leukocytes, including granulocytes, lymphocytes and monocytes may play a crucial role in restoring imbalance between proinflammatory and inflammatory cytokine levels.[14] It seems that the suppressive effect of leukocytapheresis on patients with inflammatory bowel disease is thought to depend upon the removal of activated inflammation-related cells that transfer inflammatory signals.[15] It may be that those cells removed are bound because of cell stimulation caused by microorganisms or foreign bodies. It is possible that following this procedure, the imbalance between pro- and inflammatory cytokines returns to normal. Indeed, Kawamura et al[13] described that cytokine activity in the filter and peripheral blood was normalized after the application of apheresis.

After the application of cytapheresis, Kashiwagi et al[10] found a significant suppression of proinflammatory cytokines (Tumor Necrosis Factor-alpha, interleukin-1beta, interleukin-6 and interleukin-8) produced by leukocytes, a reduction in neutrophil chemotaxis, and down-regulation of adhesion to interleukin-1beta-activated endothelial cells. They also found that after apheresis, the number of CD10-negative premature granulocytes increased, indicating increased turnover of these cells in the circulation. They suggest that selective granulocyte and monocyte adsorption is associated with modified peripheral blood leukocyte function favorable to patients with ulcerative colitis. Noguchi et al[16] found that the amount of Interleukin-4 production in peripheral blood mononuclear cells was increased after leukocytapheresis. Leukocytapheresis filter-passed lymphocytes showed increased CD4+DR- and decreased CD4+DR+ cells in comparison to peripheral blood mononuclear cells. Therefore, lymphocytes passed through leukocytapheresis filter could produce IL-4, and may lead to bystander suppression. However, it seems that the leucocytes removal filter (cellsorba) also removes and platelets. It has been shown that the platelets activation in the peripheral blood of ulcerative colitis patients stimulate the leucocytes to secrete active oxygen. Thus removal of activated platelets may result in inhibiting production of active oxygen and diminution of symptoms of inflammation.[18]

Although reperfusion injury has not been described as a major contributing factor for tissue damage in IBD, it has recently been found that leukofiltration may reduce reperfusion injury and rectal bleeding in inflammatory bowel disease.[19]

Finally, modulation of leukocyte enzyme activities is one of the main effects of leukocytapheresis therapy and alteration of granulocytes, monocytes and lymphocytes in patients with rheumatoid arthritis.[20] In this study treatment resulted in removal of 96% of granulocytes, 98% of monocytes and 61% of lymphocytes. The elastase activity of granulocytes was increased 4 weeks after the last session only in responders. However, dipeptidylpeptidase IV activity of lymphocytes was low at 4 weeks after the last session in responders.

Despite the fact that the exact mechanism by which leukocytapheresis exerts its beneficial effect in patients with IBD remains unknown, it seems that immunomodulation induced by the apheresis of the responsible inflammatory cells is the main mode of action.

Clinical results

a) ulcerative colitis

So far, seven studies[2,7-9,13,20,21] relating to patients with

steroid-dependent or resistant ulcerative colitis were found to contain data available for evaluation. As shown in table 1, a total number of 127 patients were treated. Remission was achieved in 110 (87%) (after application of one to five sessions) a proportion which could be characterized as quite significant. However, the relapse rate following cessation of treatment was relatively high (42% of those with initial response, relapsed during the follow-up period of up to 12 months) (Table 1).

b) Crohn's disease

Quite a few patients with Crohn's disease have been treated with leukocytapheresis, compared with ulcerative colitis[13,22-24] (Table 2). However, the remission rate was similar to that of ulcerative colitis (77%), while the proportion of patients who remained in remission during the follow-up period was almost identical (54%). In a study from France[22], lymphapheresis was performed in 12 patients with exacerbation of Crohn's disease who achieved remission with steroids. Treatment resulted in a 100% withdrawal from steroids, compared to10 out of 15 in the control group. However, after 18 months the cumulative relapse rate was 82% in the lymphapheresis group and 62% in the control group. So lymphapheresis did not prevent the occurrence of early relapse in patients with Crohn's disease.

Table 1. Clinical results of leukocytapheresis on patients with Ulcerative colitis

Author	Year	No of patients teated	Remission	Unchanged	Number of sessions	Remission on follow-up
Kawamura	1999	12	11 (92%)	1 (8%)	1	NDA
Sawada	1995	25	21 (84%)	4 (16%)	5	19 (76%)
Ayabe	1997	14	13 (93%)	1 (7%)	1	13 (93%)
Ayabe	1998	23	18 (78%)	5 (22%)	1	NDA
Amano	1998	37	34 (92%)	3 (8%)	3	28 (76%)
Sasaki	1998	9	6 (67%)	3 (33%)	5	NDA
Kondo	2001	7	7 (100%)	0 (0%)	1	4 (57%)
Total	1995-2001	127	110 (87%)	17 (13%)	1-5	64 (58%)

NDA = no data available

Table 2. Clinical results of leukocytapheresis on patients with Crohn's disease

Author	Year	No of patients treated	Remission	Unchanged	Number of sessions applied	Remission on follow-up
Kawamura	1999	4	4 (100%)	0 (0%)	1	NDA
Lerebours	1994	12	12 (100%)	0 (0%)	9	10 (83%)
Sawada	1995	19	16 (84%)	3 (16%)	1	12 (63%)
Kosaka	1999	18	9 (50%)	9 (50%)	1	NDA
Total	1994-1999	53	41 (77%)	12 (23%)	1-9	22 (54%)

NDA = No data available

Complications

The complications of leukocytapheresis are shown in table 3. All side-effects were of a mild degree and transient. Thus, the procedure must be considered as safe

Table 3. Complications appeared during leukocytapheresis

Author	Percentage
Sawada et al (1995)	No significant complications were recorded 6.4% (21/328 procedures)
Kosada et al (1999)	Complications (all mild and temporary) Abdominal discomfort nausea allergic reaction sensory disturbances of tongue and lips nasal obstruction cardiac symptoms of palpitations headache dizziness low fever chill

and without significant side-effects.[25-29]

Conclusion

The use of leukocytapheresis in the treatment of IBD seems to achieve the best results in patients with ulcerative colitis. A draft of guidelines concerning treatment of ulcerative colitis and the timing of possible application of leukocytapheresis is given in figure 1. Certainly, many modifications or alternative strategies including administration of heparin, cyclosporin, anti-TNF-a antibody etc. can be applied. However, this draft could be useful if the procedure and the required facilities are available. Leukocytapheresis seems to be quite a promising modality requiring further investigation.

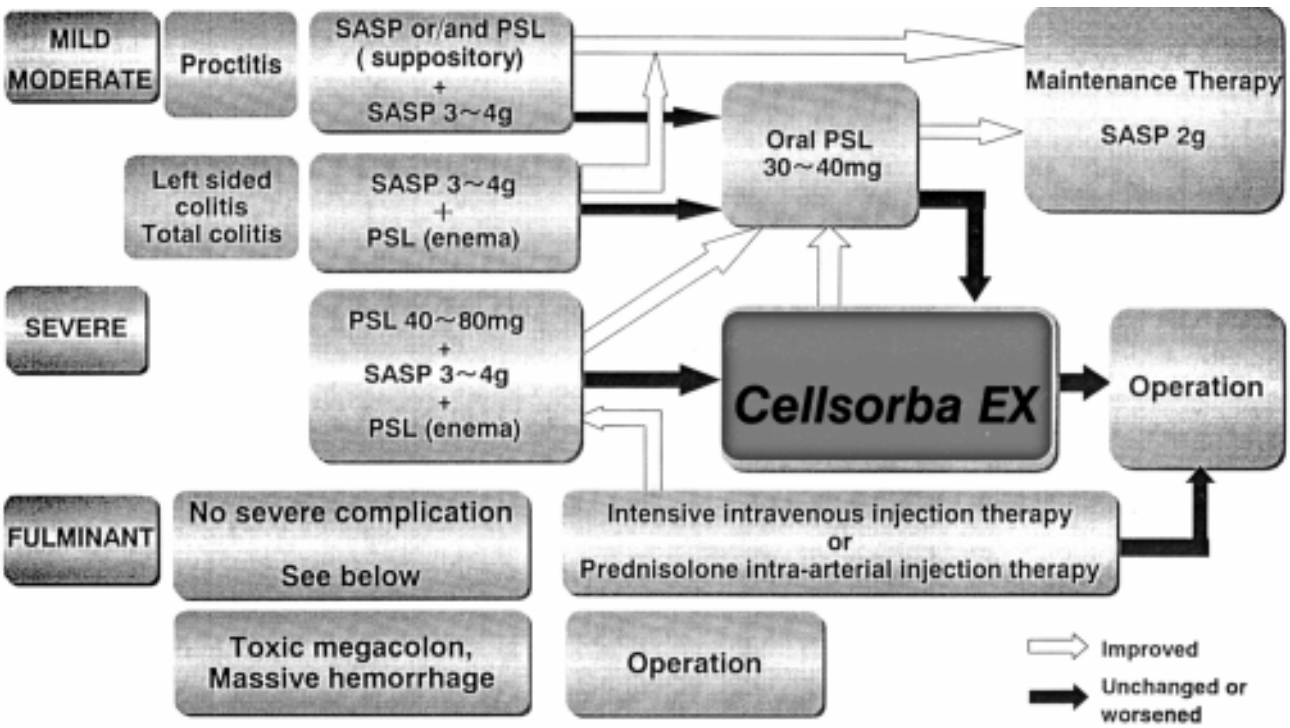

Figure 1. Draft of the Guidelines for the Treatment of Ulcerative Colitis.

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