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Atherosclerosis Supplements 14 (2013) 83−87

ATHEROSCLEROSIS
SUPPLEMENTS

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Acute and chronic effects of therapeutic apheresis

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Abstract

In most patients only a few sessions of apheresis treatment are necessary to see the benefit. This is the case of immunological diseases when the production of a pathologic component is limited in time or in microcirculation disturbances when changes of vascular function may occur. In the first instance the acute effect is likely due to the removal of the corresponding antibody, while in the second case the improvement of the endothelium-dependent vasodilation and the reduction of blood viscosity play a major role. In long-term treatment, as in the case of patients affected by familial hypercholesterolemia, the chronic effects of apheresis may lead to the repair of morphological alterations in the vascular wall. We report the recovery from ulcers in two hemodialysis patients suffering from peripheral arterial disease as the result of twenty-two sessions of rheopheresis. The reasons that justify these chronic actions may involve pleiotropic effects that are different according to the apheresis technique used.

Keywords: Therapeutic apheresis; Pleiotropic effects; Rheopheresis; Peripheral arterial disease

1. Introduction

Most patients treated with therapeutic apheresis (TA) undergo a limited number of sessions. According to the International Register of Apheresis report on the frequency and percentage of treatments registered per patient, the average is of 1−5 treatments for more than 80% of plasma treatment procedures [1]. Furthermore, the last version of ASFA guidelines [2] confirms that in most diseases a few number of sessions, almost always less than 10, are enough to achieve a positive outcome.

This is due to the fact that, for most diseases, the pathogenic agent responsible for the problem has a limited production over time, being almost always a dysfunctional immunologic component. In this case, we are bound to think that the apheresis acute effects, related to the removal of the harmful component, and the cure to the problem are strictly connected.

Due to a mutation in the corresponding gene, patients with familial hypercholesterolemia have a permanently high LDL-cholesterol plasma concentration. Therefore, constant TA treatments are required to keep these levels within a normal range. In this case, the chronic effects of TA on the cardiovascular system are not confined to lipid reduction, but may also include an increasing number of pleiotropic aspects [3,4].

In regards to these additional effects, the question is whether they may exert an active role in vascular protection and which one, among them, could be more effective in this function. This issue is of crucial importance when applying TA to treat microcirculation disturbances, since in this

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http://dx.doi.org/10.1016/j.atherosclerosissup.2012.10.018

context the intent is not to reduce lipids but to improve vascular perfusion. Even though the different LDL-apheresis methods available on the market have similar effects as regards to lipid reduction, the same cannot be said for pleiotropic effects. Unfortunately, only few comparative studies regarding the different LDL-A methods have been carried out, most of which did not follow the evidence-based medicine framework. Nevertheless clear differences in terms of pleiotropic effects were observed. A comparative study addressing the different pleiotropic effects on the coagulation system shows that, beside a marked difference in fibrinogen reduction compared to immune-adsorption, dextran-sulfate adsorption causes a significant decrease in prothrombin time and an increase in activated partial thromboplastin time [5]. A similar difference was also evident when comparing DALI to HELP, only to quote the most relevant ones [5]. Even for the adhesion molecules, different capacity of subtraction was discovered according to the apheresis system used [6]. More recently, a comparison among three different columns during LDL-apheresis, namely Liposorber D, Liposorber LA-15 and Cascadeflo EC-50W, showed significant differences regarding fibrinogen, no differences regarding thrombin–antithrombin complex and one difference between DL-75 and EC-50W regarding plasminogen activator inhibitor-1 [7]. Also for homocysteine, the percentage of reduction was different among the three methods. Changes of systemic oxidative stress markers induced by four different techniques were also found by Julius and colleagues [8], with DALI apheresis system associated with the lowest systemic oxidative burden and HELP the most effective in the reduction of CRP. Finally, the proteomic analyses of the column-bound proteins, eluated by three different LDL apheresis columns, revealing the highest number of protein spots in DALI-treated patients (1001), followed by HELP (881) and DFPP (535) [9]. Following these considerations, if we decide to use an apheresis procedure with the aim to treat a microcirculation disturbance in patients not affected by familial hypercholesterolemia, we should know which technique has the most effective pleiotropic action. Moreover, in trying to correct microcirculation disturbances it is necessary to address two main issues: when to start the treatment and for how long to proceed.

2. Acute and chronic effects of TA

Before attempting to give an answer, it would be better to take into account that the acute effects of TA manifest themselves shortly after a few number of sessions. We can call these acute or functional effects, such as those able to improve hearing ability in SHL [10], visual capacity in NAION [11] or reduce pain in the lower limbs or increase the walking distance ability in peripheral arterial disease (PAD) [12].

These acute effects, due to the fact that they become evident already after one of few sessions, seem to be limited essentially to an endothelium-dependent vasodilation, demonstrated at forearm [13], coronary [14] and retinal level [15]. The vasodilatatory effect is more than likely due to a drastic reduction in oxidized LDL, which stimulate endothelial nitric oxide synthase activity, consequently increasing production of nitric oxide. This phenomenon was also shown in non-hypercholesterolemic patients affected by SHL, following rheopheresis treatments [16].

Beside endothelium-vasodilation, among the acute effects of TA, we also need to consider blood viscosity reduction, which improves microcirculation perfusion, as formulated by Hagen-Pouiselle law.

In this context fibrinogen has often been described as the most important protein in erythrocyte aggregation, thus increasing whole blood viscosity. At fibrinogen concentrations lower than 117 mg/dl, whole blood viscosity at all shear stress levels is lower than the viscosity of a suspension of erythrocytes in physiological saline solution [17].

Close to fibrinogen, some authors consider alfa2-macroglobulin an even stronger inducer of RBC aggregation [18].

Adhesion molecules are also involved in microcirculation perfusion. Changes in hemodynamics during leucocyte-endothelium adhesion can be accounted for by a decrease in the effective diameter due to obstruction of the lumen by WBCs. These effects have been studied in mesenteric arteries of cats, where an increase in flow resistance of up to 150% has been observed in vessels with a 25 μm diameter [19].

However, being essentially linked to a functional action, these acute effects can last only a short time after suspending the apheresis treatment, as we verified in a six-month follow up of patients affected by NAION [20].

On the other hand, a long-term treatment with apheresis procedures might act on the morphological component of the vascular damage, leading to an improvement of artery occlusion, with consequent ulcer healing [21], a reduction in atherosclerotic plaque area and coronary stenosis [22], or carotid intima-media thickness reduction [23].

The mechanisms underlying the chronic effects of apheresis are still an object of debate.

Recently, an influence on endothelial progenitor cells, that are able to proliferate and repair the vascular damage, has been proposed in two studies [24,25].

A sustained inhibition of oxidized-LDL cholesterol particles has also been indicated to explain the recovery of ulcers in dialysis patients affected by PAD who underwent a long-term treatment with LDL-apheresis [26].

3. TA and recovery from ulcers

In the attempt to clarify whether there is still time for successful intervention when ulcers appear, we administered a cycle of rheopheresis in two severe cases of PAD affecting patients in hemodialysis who had just undergone

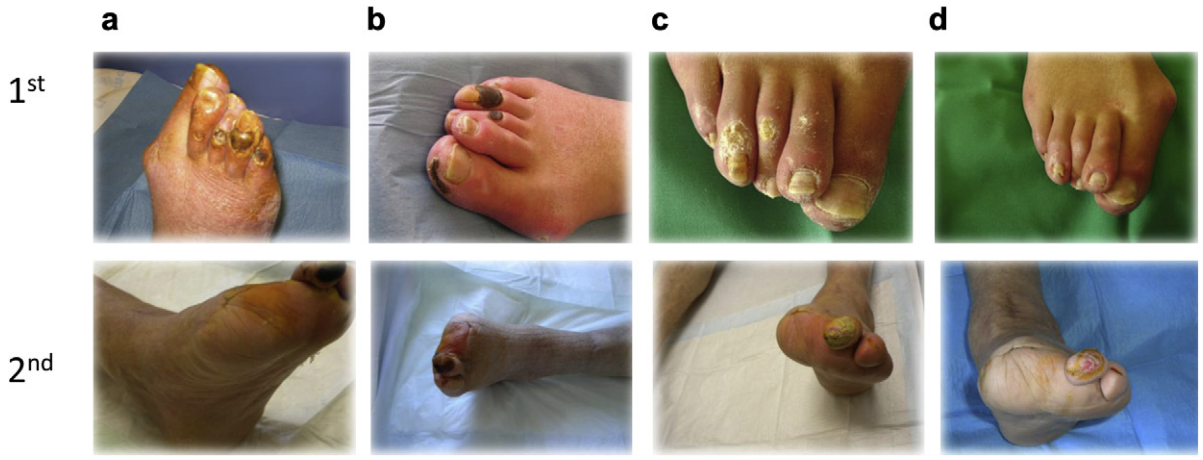

Fig. 1. Grading of scarring over the ulcers until complete healing during the course of apheresis in the two patients. a) baseline; b) after 6 sessions; c) after 19 sessions; d) after 22 sessions.

Table 1
Schedule of the apheresis treatment.

Schedule of treatment
• 3 sessions a week for the first two weeks (1 plasma volume) = 6
• 2 sessions a week in the third and fourth week (1 plasma volume) = 4
• 1 session a week in the second month (1 plasma volume) = 4
• 1 session a week in the third and fourth month (1.5 plasma volume) = 8
• Total sessions = 22 in 4 months

an amputation surgery to one foot. The two patients gave their informed consent to the apheresis treatment and the ethical committee approved this therapeutic approach. Fig. 1a shows the actual state of the remaining foot about to be amputated because despite the traditional treatment (platelet antiaggregant, statins, pentoxyfillin) they showed no sign of improvement. The total number of sessions was 22, administered in 4 months, according to the schedule shown in Table 1, with the treatment of 1 plasma volume for each session. The photographic documentation shows what happened after six sessions (Fig. 1b), fourteen sessions (Fig. 1c) and also the end of the cycle, namely after 22 sessions (Fig. 1d) when both patients experienced a complete recovery. At this point in the treatment, we made the decision to stop treating the first patient but to continue the procedure once a week for another year with the second patient. After the first patient had completed the apheresis treatment for a total of 16 months, all treatments were ended. We then compared the outcome for both patients after a two-month gap and, as it can be seen in Fig. 2, in the first patient only two months after the end of apheresis new ulcers reappeared, while in the second patient the situation remained unchanged, despite the fact that the second patient had stopped receiving treatment 18 months before.

In the attempt to understand what may have contributed to the disparity between the two outcomes, we compared the two patients in terms of cardiovascular risk factors, finding out a marked difference in the dialytic age (first patient: 130 months; second patient: 32 months) and the presence of diabetes (present in the second patient, absent in the first). However, the main differences concerned the lab results. As it can be seen in Table 2, there were abnormally high concentrations of lipids, fibrinogen and Lp(a) in the first patient compared to the second, at baseline. By the 14th session, in the first patient the levels of lipids were significantly reduced even in pre-apheresis, except in fibrinogen

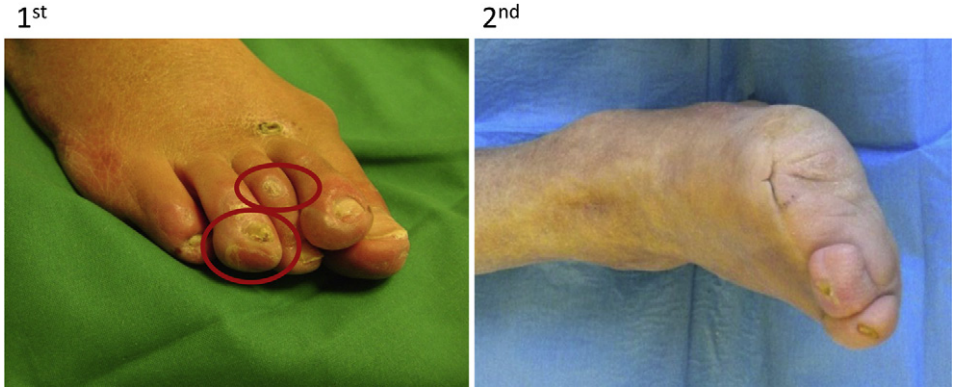

Fig. 2. 1st) First patient two months after the suspension of apheresis; 2nd) second patient eighteen months after the suspension of apheresis.

Table 2
Lab results of the two patients before and after the first apheresis session.

Parameters	First patient Ìapheresis (pre-post)		Second patient Ìapheresis (pre-post)	
Triglycerides mg/dl	540	411	118	74
Total cholesterol mg/dl	243	190	93	44
HDL cholesterol mg/dl	30	26	28	22
LDL cholesterol mg/dl	131	99	41	13
Fibrinogen mg/dl	325	227	191	82
Lp(a) mg/dl	>1000	768	216	128

(408 mg/dl). Similar concentrations of lipids were observed in pre-apheresis during the 15th month. Only fibrinogen remained critically high (547 mg/dl).

In conclusion, our experience demonstrated the effectiveness of rheopheresis in the treatment of advanced stage of PAD, with the complete recovery of ulcers after a cycle of 22 sessions, even in the diabetic patient. Although diabetes is an independent risk factor for foot ulceration in hemodialysis patients [27], it doesn't seem to have hindered ulcer healing. A possible explanation could be the strict control of glycemia observed in the patient that, beside the low level of lipids, especially Lp(a) and fibrinogen at baseline, seem to prolong the effectiveness of apheresis even after termination of treatment. Based on the aforementioned reports, the course of treatment should be personalized, according to lipids and fibrinogen concentrations in determining the schedule of the apheresis therapy.

Further studies that may take into account the previous mentioned variables can confirm the first results.

4. Conclusion

The acute and chronic effects of TA seem to be linked to different mechanisms of action. In the case of immunological diseases, as the production of the pathogenic component is limited in time, the derived benefit is likely due to the removal of this substance. In the case of microcirculation disorders, when morphological alterations of the vascular walls occur, the acute effect may only act on the functional aspect of the damage, improving hemorheology at microvascular level. A more relevant intervention aiming at operating on the vascular damage needs to extend the apheresis treatment for a longer period, with mechanisms of action still under investigation.

Conflict of interest

Ramunni is medical advisor for Asahi Kasei Medical Company from the beginning of 2012. The other authors have no conflict of interest to declare.

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