Application of LDL-apheresis and immunoadsorption in kidney diseases

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Abstract

Plasmapheresis is one of the methods of extracorporeal blood purification used for many decades for the treatment of different kidney and extrarenal diseases, mainly of autoimmunological nature. The main disadvantage of this method is the lack of selectivity and the risk of infections associated with plasma used for supplementation. Hence, the efforts are made to establish an alternative blood purification treatment that might be used in renal diseases instead of plasmapheresis. These alternative methods should be more selective in certain pathogenic factors elimination and result in less risk for patient, both acute and delayed. Recently two such methods were applied more frequently to everyday nephrological practice, i.e. LDL-apheresis and immunoadsorption. The present paper aims to review the current state of knowledge regarding use of two mentioned methods in kidney diseases. Despite their very high costs both of them if used early in certain, refractory nephropathies may ameliorate their clinical course and significantly improve the prognosis. In addition they may significantly reduce the overall costs of therapy due to avoidance of unnecessary immunosupression, prolonged hospitalization and finally – costs of postponed renal replacement therapy.

Key words: plasmapheresis, LDL-apheresis, immunoadsorption, kidney diseases, renal transplantation.

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Introduction

Plasma exchange (PE; plasmapheresis) belongs to the group of methods commonly called extracorporeal blood purification techniques. They are used not only for the treatment of kidney diseases, but also in many other disorders, mainly from the area of neurology and toxicology. In some diseases this method was proven to be very effective (anti-GBM glomerulonephritis, Guillan-Barre syndrome, hemolytic-uremic syndrome, recurrence of certain glomerulopathies in transplanted kidney), whereas in others its effectiveness remains doubtful and lacks good support with prospective clinical trials. Although relatively safe, traditional plasma exchange carries certain risk for the patient, both acute (related to the procedure itself), as well as delayed (risk for transmission of certain viral infections with the fresh frozen plasma used as the supplement fluid appears the most important one). Unfortunately, during therapeutic elimination of immunoglobulins or immune complexes that might be involved in the pathogenesis of the disease, this method exposes the risk related to non-selective, uncontrolled elimination of other circulating agents, including blood coagulation factors, hormones etc. Thus the researchers focused on the development of new techniques that might provide more selective techniques targeting certain circulating pathogenic agents without the concomitant removal of physiological factors.

Among methods used in extracorporeal blood purification two of them attract a special attention from nephrologist's point of view as potential tools in the treatment of renal diseases. These methods are LDL-apheresis and immunoadsorption.

LDL-apheresis

Selectivity of LDL-apheresis

Different methods of apheresis possess different selectivity for pathogenic factor removal. The simplest one is of course plasmapheresis with no selectivity at all. Double-filtration plasmapheresis (DFPP) is also characterized by relatively low

selectivity, as plasma proteins are eliminated depending on their molecular weight only. Another method frequently used, heparin-induced extracorporeal lipoprotein precipitation (HELP) allows eliminating not only LDL-cholesterol, but also other factors that precipitate in low pH in the presence of heparin. As these factors include lipoprotein (a) and fibrinogen, this cannot be considered as a side effect, but rather an additional benefit of the procedure. Indeed, HELP is very efficient in elimination of both mentioned proatherogenic agents. The efficacy of fibrinogen elimination (highest among all extracorporeal LDL-cholesterol removal techniques) limits the volume of plasma that may be processed during single procedure to 3000 ml per session to avoid pronounced fibrinogen depletion.

The elimination of different plasma proteins deserves special attention in case of dextran sulphate, the basic ligand used for LDL-apheresis. In his interesting review Kojima divided these substances depending of the mode of interaction with the column into four groups: proteins containing apolipoprotein B (LDL-cholesterol, lipoprotein a), proteins that become activated in the initial contact phase of the intrinsic coagulation pathway (prekallikrein), lipophilic proteins that adhere to the phospholipid portions of LDL-cholesterol already bound to the column (coagulation factors VIII, V, VII, X, vitamin E) and other adhesive proteins (von Willebrand factor, fibronectin) [1]. Again, the elimination of most of mentioned proteins is rather positive, than undesirable effect, as most of them are proatherogenic. As it has been shown in comparative studies, all LDL-apheresis techniques to the different extent eliminate also HDL-cholesterol and triglicerydes, although these effects are transient [2].

LDL-apheresis in refractory hypercholesterolemia

Although the aim of this paper is to review the role of LDL-apheresis in renal disease, we should also refer briefly to its use in other diseases. Originally, LDL-apheresis was established to treat familiar homo- or heterozygous hypercholesterolemia refractory to conventional treatment (i.e. diet plus lipid-lowering drugs, mostly HMG-CoA inhibitors). The data available on the influence of LDL-apheresis on lipid profile and on the possible clinical symptoms, although convincing, are usually obtained in small groups of patients. It is obvious, as apheresis may be performed only in highly selected populations, in which both diet and lipid-lowering drugs appeared to be ineffective [2-5]. Another important consideration is that these studies cannot be blinded for obvious reasons [2]. Nevertheless most of the trials provide the data that confirm the efficacy of LDL-apheresis, especially when combined with pharmacological treatment. This efficacy is obtained not only in terms of serum lipid concentration lowering, but also in the prevention of atherosclerosis progression, decrease in the onset of new cardiovascular and cerebro-vascular events, as well as substantial reduction of mortality [2-5]. Some studies suggest that even slight regression of atherosclerosis may be achieved under the treatment with LDL-apheresis [3,5].

LDL-apheresis in kidney diseases

Initial concept for LDL-apheresis was to use it as a lipid-lowering treatment (lipoprotein elimination) in refractory (mostly familial) hypercholesterolemia. However, this method was also proven to be effective in the treatment of nephrotic syndrome (NS). The use of this method in NS is logical, as this group of diseases manifests with severe dyslipidaemia. Interestingly, LDL-apheresis was effective not only in symptomatic lowering of plasma lipids, but also influenced the course of nephropathies of different origin. In this review we aimed to focus mostly on the impact of LDL-apheresis on the clinical course of various primary and secondary nephropathies.

There are only few indications in renal patients, in which the usefulness of LDL-apheresis seems to be proven, although mostly in non-randomized observations performed in small-sample size populations. These indications include: primary focal segmental glomerulosclerosis (FSG), recurrence of FSG in transplanted kidney and lupus nephritis. Anecdotal reports indicate that many other glomerular diseases irrespectively from the type might be successfully treated with LDL-apheresis, when other therapies were ineffective.

Yokoyama and co-workers showed a significant decrease of daily protein loss and increase in GFR after the course of LDL-apheresis among 14 patients with FSG refractory to previous steroid treatment. Six procedures performed over 3 weeks were sufficient to achieve the improvement in GFR, the reduction of daily protein loss and normalization of lipid profile for more than 6 months of follow-up. In addition, repeated biopsies performed 3 months after LDL-apheresis therapy revealed the regression of morphological lesions when compared to initial (pre-treatment) samples. As one could expect the response to treatment was better in patients with less severe sclerosis on initial biopsy, but with more severe nephritic syndrome at the treatment initiation [6]. In the study of Musso et al. an amelioration of symptoms of nephrotic syndrome due to FSG or minimal-change nephritis resistant to previous treatment was accompanied by decreased intensity of mesangial staining for ApoB and reduced number of macrophages infiltrating the glomeruli in patients responding to LDL-apheresis therapy [7]. Many case reports confirm, that LDL-apheresis may be successfully employed in the treatment of FSG and that along with lowering of serum lipid profile proteinuria decreases, serum total protein and albumin levels increase and renal function improves [8,9]. The concomitant use of HMG-CoA inhibitors may additionally enhance the effect of LDL-apheresis [9,10]. The use of mentioned drugs is also advisable to avoid a rebound effect (i.e. the return of serum lipids to pre-treatment level after certain period of time). In addition, this group of drugs could probably improve the clinical course of certain nephropathies in lipid lowering-independent mechanisms, probably associated to its anti-inflammatory and antithrombotic properties.

The employment of LDL-apheresis in lupus-associated nephropathy should probably be limited only to patients who are resistant to other therapies and those with rapid clinical and morphological progression to renal failure. Daimon and co-workers described such a patient with rapidly progressing glomerulonephritis in the course of systemic lupus, with presence of crescents in 11 out of 22 glomeruli in renal biopsy specimen, who needed dialysis due to rapid deterioration of renal function. The initial use of plasmapheresis was sufficient to recover renal function and quit renal replacement therapy, although did not protect the patient from severe nephrotic syndrome. This

state was further treated with LDL-apheresis using Liposorba columns and later on – with DNA-adsorption using Selesorb columns [11]. This case report provides an excellent example for an 'integrated' extracorporeal treatment using four (including hemodialysis) blood purification techniques for treatment of severe systemic lupus.

LDL-apheresis may also be effective in the treatment of nephrotic syndrome associated with the recurrence of glomerulonephritis in transplanted kidney. This method appears to be especially effective in recurrent FSG [12].

Effectiveness of LDL-apheresis was also proven in other diseases associated with nephrotic syndrome resistant to immunosuppressive therapy, such as minimal change nephritis although vast majority of reports are limited to small groups of patients or even single cases [13-15]. Interestingly, LDL-apheresis may also ameliorate renal function in diabetic nephropathy [16,17].

LDL-apheresis: mechanisms of action in glomerular diseases

Several mechanisms in which the lowering of serum lipids may improve kidney function and slow down or even reverse the progression of renal insufficiency were proposed. LDL-cholesterol in its oxidized form may induce the formation of foam cells, thus accelerating inflammatory process and glomerular damage [6,7,15,18]. Another possible mechanism is binding of lipoproteins to polyanionic glycosaminoglycans in the mesangial matrix and glomerular basement membrane with further modification of their structure, electrical charge, and in consequence – permeability [19]. Oxidized LDL particles and lipoprotein (a) stimulate renin release by the juxtaglomerular cells, which may additionally contribute to the progression of renal failure in both hemodynamic and inflammatory mechanism (angiotensin II is one of the potent stimuli of TGFβ release, which in turn is the most important factor that accelerates renal interstitial fibrosis) [19,20]. On the other hand, reduction in proteinuria, despite the mechanism, diminishes LDL-cholesterol synthesis in nephrotic syndrome [10].

Although relatively selective, LDL-apheresis removes also coagulation factors V, VIII and von Willebrand factor. In addition, after LDL-apheresis the significant reduction in urinary excretion of thromboxane A_2 and B_2 was noticed. These changes suggest that improvement of renal function after the course of treatment with LDL-apheresis may at least in part depend upon the improved blood rheology in renal microcirculation [14,15].

Interesting observation was made by Muso et al., who found, that the treatment with LDL-apheresis not only increases creatinine clearance in patients with initially impaired renal function, but also leads to substantial decrease of abnormally high glomerular filtration rate to the normal range in nephrotic subjects [15]. This observation is very important, as the glomerular hyperfunction (hyperfiltration) is one of the important factors responsible for glomerular damage.

It has been proposed, that lipids removal may increase the response to concomitantly used immunosuppressive therapy [6, 14]. As it was suggested, after LDL-apheresis an up-regulation of receptors for steroids may occur [14,15]. Cyclosporin-LDL complexes are also bound to LDL receptors, hence the removal of lipids with LDL-apheresis may increase the availability of this drug [22].

Another mechanism that leads to amelioration of kidney function after LDL-apheresis in different nephropathies may be the improvement of endothelium-dependent vasodilatation after this procedure noticed in hypercholesterolemic patients [23]. Vasodilatatory properties of blood vessels are seriously compromised in patients with renal diseases; the restoration of this function with LDL-apheresis may possibly contribute to the improvement of renal function due to improvement of local blood circulation.

The real efficacy of LDL-apheresis is largely confounded by concomitant treatment with immunosuppressive drugs. From this point of view an interesting observation was maid by Yokoyama et al., who performed LDL-apheresis in patient with FSG previously naive to immunosuppression [24]. Patient described in the cited case report experienced marked improvement in renal function and significant decrease in urinary protein loss from initial 5.31 to 0.87 g/day after initial course of 6 LDL-apheresis procedures without concomitant treatment with immunosuppressive drugs. This clinical improvement was accompanied by regression of some histological lesions in repeated kidney biopsy. Patient was maintained on LDL-apheresis treatment alone performed twice a month [24]. Of course this data, although very interesting, cannot suggest the use of LDL-apheresis alone as a routine treatment. Nevertheless, this observation suggests that the discussed method may be useful also without concomitant immunosupression.

Immunoadsorption

Another technique that recently deserved special attention of nephrologists is immunoadsorption (IA). This technique allows eliminating immunoglobulins and other circulating agents that might be involved in the pathogenesis of different diseases, mostly of immunological origin, in the relatively selective manner. Selectivity is largely dependent on the type of the membrane and especially – the type of ligand used for adsorption. These adsorbents include staphylococcal protein A (SPA), tryptophan, phenylalanine, monoclonal sheep anti-IgG-human immunoglobulin, dextrane sulphate [25-29]. The types of membranes and ligands used for LDL and IA as well as selected indications for treatment in renal and extrarenal diseases are summarized in *Tab. 1*. Depending on the type of the ligand used and the type of circulating pathogenetic factor the elimination this factor may be based on immunological, chemical or electrostatic interaction. Most of the IA techniques utilizing mentioned ligands are designed to eliminate circulating antibodies and immune complexes. Indeed, these methods may really be selective in elimination of certain plasma components. As it has been shown for dextran sulphate in *in vivo* experiment, this ligand was able to adsorb 62% of passed anti-DNA antibody, 47% of cardiolipin and 26% of immune complexes, whereas no adsorption of total protein, albumin, immunoglobulin G nor C3 complement component was noticed [30]. Of course this theoretical selectivity is not fully

sustained *in vivo* – the substantial amounts of IgG or albumin are also lost during the procedure [27,31]. Interestingly, as it was shown in patients with lupus nephritis, IA possesses also immunomodulatory properties, as it is able to restore the initially decreased complement level [32,33]. IA selectivity may be further improved using more specific ligands, such as anti-β_2-microglobulin antibody or hexadecyl alkyl chains containing columns (designed exclusively to eliminate β_2-microglobulin in dialysis patients), or acetylocholine receptor peptide columns in the treatment of myasthenia [28,34,35]. Immunoadsorption using specific LDL-apolipoprotein B binding antibodies or dextran sulphate are also used for the LDL-chlesterol elimination, as it was discussed in the previous section of current review.

Immunoadsorption in primary and secondary nephropathies

Similarly to the statement made when discussing LDL--apheresis, also the use of IA is especially important in fast – progressing, treatment – resistant nephropathies with poor renal and overall prognosis. This is especially true for those nephropathies which manifest clinically as rapidly progressive glomerulonephritis and morphologically as crescentic nephropathy. In one of the early reports, Palmer et al. described significant improvement of renal function in 10 patients with crescentic glomerulopathy already on dialysis. In all cases immunoadsorption coupled with immunosupression resulted in recovery of renal function and dialysis – independency. Simultaneous resolution of glomerular crescents was observed [36]. Similar results were also presented in the number of case reports, describing both patients with primary crescentic nephropathies and Goodpasture syndrome [26,37]. As one could expect the presence of 'early', cellular, but nor fibrous crescents is probably the *sine qua non* condition for therapeutic success in IA, as it happens for 'classical' immunosupression.

Large group of diseases that may manifest as crescentic (rapide progressive) glomerulonephritis are ANCA-positive vasculitides. Matic et al. reported 3 cases of Wegener's granulomatosis with severe renal and other systemic involvement successfully treated with IA. In all patients the clinical improvement was accompanied by complete elimination of circulating c-ANCA antibodies [25]. However, in the prospective randomized trial comparing IA versus plasmapheresis in the treatment of rapidly progressive glomerulonephritis (RPG) in patients with at least 50% of glomeruli with crescents Stegmayr and co-workers failed to demonstrate any difference in patients' outcome between the two treatment groups [38].

The studies performed to date clearly indicate that 'classical' plasmapheresis is not effective in the treatment of lupus erythematosus. Several studies showed its relative usefulness as a symptomatic treatment relieving acute symptoms of flares, but none of them was able to demonstrate the independent impact of PE on survival. In opposite, IA appeared to be useful in the treatment of severe cases of systemic lupus, probably because it allows treating much larger volumes of plasma. Although the large prospective studies are still lacking, the preliminary clinical reports are very promising. Remission was achieved in 7 out of 8 patients with drug – resistant SLE treated with immunoadsorption onto protein A, reported by Braun and co-workers. In all patients the substantial amelioration of symptoms from different body systems was achieved, including arthritis and polyserositis, decline of proteinuria and serum creatinine concentration. Clinical improvement was accompanied by significant decrease of circulating plasma autoantibodies. Interestingly, IA led to restoration of initially decreased complement levels [32]. The same authors described the case of critically ill patient with lupus (renal WHO class IVd), non-responding to any drug treatment applied. She was successfully treated with IA after previous discontinuation of all immunosuppressive agents when became dialysis dependent and presented with grand mal seizures. After two weeks of repeated IA dialysis treatment was stopped; renal biopsy was performed 9 months later and only minor morphological abnormalities were found [33]. Another report showed significant improvement in overall SLE disease activity index and in most of the clinical manifestations such as skin lesions, leukopenia and proteinuria in 19 SLE patients treated with mean number of 3.7 IA procedures using dextran sulphate as a ligand [39]. The use of IA together with steroids and/or cyclophosphamide allowed for significant reduction of total dose of immunosuppressive agents and appeared to be an additive synergistic therapy [39].

Effectiveness of IA in elimination of anticardiolipin antibodies appears to be a major advantage in the treatment of SLE (and possibly – in primary anti-phospholipid syndrome). The onset of anti-phospholipid syndrome leads to very serious complications of the disease, including marked mortality among patients, mainly due to thrombosis, and habitual abortions in pregnant women. Hence, the new alternative for treatment of this dangerous disease may be of great importance in terms of possible reduction of mortality and improved outcome for pregnancies [33,40,41].

The interesting results of the treatment with IA in nephrotic syndrome of primary and secondary origin were presented in 1999 by Esnault et al. They used repeated IA to protein A columns in 9 patients with membranous glomerulonephritis, IgA glomerulonephritis, amyloidosis and diabetic nephopathy. Significant reduction of proteinuria from the mean 12.6 ± 5.49 to 3.35 ± 2.2 g/24 h (75.4% decrease) was achieved. It is worth to emphasize that authors obtained significant amelioration of proteinuria also in the disease of non-immunological pathogenesis, namely diabetic nephropathy [31].

Immunoadsorption in solid organ transplantation

Except of the usefulness of IA in the treatment of 'native' kidney diseases this technique seems to be promising in renal transplantation. First, the discussed method may help preparing high-risk patients for transplantation. Haas and colleagues used IA to lower the level of panel reactive antibodies (PRA) in patients awaiting retransplantation. They performed up to 24 sessions in pre- and early posttransplant period in 20 highly sensitized patients (median PRA 87%), achieving excellent patient and graft survival [42]. Second, severe complications of transplantation may also be managed using IA. Boehmig et al. treated acute humoral renal transplant rejection in ten patients displaying C4d deposits in peritubular capillaries on renal biopsy, using immunoadsorption onto protein A (median number of sessions equaled 9), together with standard anti-

Table 1. **Selected ligands used for immunoadsorption and apheresis, their trade names and indications for clinical use**

Procedure	Ligand	Trade name/Manufacturer	Therapeutic Indication/Factor eliminated
LDL-apheresis (HELP)	Physical factors (low temperature), heparin	B. Braun	Elimination of LDL-cholesterol, lipoprotein (a) and fibrinogen
LDL-apheresis	Anti-Apo B antibodies	DALI system, Fresenius	Lipoprotein elimination
	Dextran sulphate (LA-15, LA-40)	Liposorba, Kaneka	Elimination of lipoproteins, LDL-cholesterol, apolipoprotein B, lipoprotein (a)
Immunoadsorption	Dextran sulphate	Selesorb, Kaneka	Non-specific binding and elimination of antibodies and immune complexes; used in myastenia, Guillain-Barre syndrome, prophylaxis of acute rejection in AB0 blood groups incompatibility and in the presence of anti-HLA antibodies, immunovasculitis, Goodpasture disease and syndrome, SLE, habitual abortion, antiphospholipid syndrome, infiltrative ophtalmopathy in Graves-Basedow syndrome, primary and recurrent FSG (permeability factor elimination)
	Staphylococcal protein A (SPA)	Immunosorba, Fresenius Prosorba, Kaneka	
	Anti-IgG antibodies	Therasorb, PlasmaSelect; Baxter	
	Fenylalanin	PH-350	
	Tryptophan	TR-350	myastenia, autoimmune polineuropathy, rheumatoid arthritis (rheumatoid factor)
	Polimyxin B		Sepsis (elimination of endotoxines, cytokines, chemokines)
	Albumin	MATISSE, Fresenius	
	Hexadecyl alkil polymer	Lixelle, Kaneka	β_2M-amyloidosis
	Monoclonal anti-β_2M antibody; recombinant fragment scFv of anti-β_2M antibody		
	Fibrinogen-binding pentapeptide	Rheosorb, PlasmaSelect	Fibrinogen, fibrin, fibrinogen degradation products; impaired blood rheology, hypercoagulability
	Anti-acetylocholine receptor antibodies	Medisorba MG, Kuraray Medical Inc.	Myasthenia gravis
	Resins: Amberochrom Amberlit		Sepsis/removal of: 80% TNFα 100 IL-1α, IL-1β, IL-8 40% TNFα

rejection therapy. In eight out of 10 treated patients prolonged normalization of graft function for a mean period of 14.2 +/- 7.1 months has been achieved [43].

The recurrence of certain nephropathies (or their de novo onset) appears to be an emerging problem in renal transplant recipients. Although not routinely used in primary FSG, immunoadsorption seems to be promising in the treatment of recurrent FSG after renal transplantation. The recurrence of mentioned nephropathy is related to not completely recognized circulating 'permeability factor' that impacts on permeability properties of glomerular filtrating membrane. Bussemaker et al. described the patient with severe nephrotic syndrome (urinary protein loss of up to 35 g/d, with advanced glomerular lesions on graft biopsy seven months after transplantation), in which IA to tryptophane (11 consecutive sessions) was able to reduce proteinuria to 2.0 g/d and to restore serum albumin level and normal renal function [27]. Other authors confirmed the successful outcome of recurrent FSG in renal transplant recipients treated with IA [44,45]. Belson et al. described a 9-years old patient who started plasmapheresis since 12th posttransplant day because of severe nephrotic syndrome due to recurrent FSG, followed by immunoadsorption on protein A column since 8th post-transplant month and remained on this treatment for up to 60 months [46].

Initial results with this procedure are so encouraging, that in the EDTA guidelines for renal transplantation released in the year 2000 immunoadsorption on protein A or anti-IgG column as well as plasmapheresis were recommended as measures for recurrent FSG in renal transplant recipients (Guideline IV.2.5.A) [47].

"Non-renal" indications for immunoadsorption

Another promising indication of immunoadsorption may be the removal of β_2-microglobulin. This agent is responsible for many serious complications in patients on long-term dialysis. 'Traditional' hemodialysis treatment with bioincompatible membranes is not sufficient enough to eliminate this low molecular weight protein. The experimental use of the column containing anti-human β_2-microglobulin antibodies in vitro was sufficient to eliminate this agent to the level below the detectable limit of assay [34]. Another method for selective elimination of β_2-microglobulin, based on hexadecyl alkyl chains was also effective in adsorption of endotoxins in an in vitro model [35].

Protein A-based IA was also effective in the removal of anti-platelet antibodies in idiopatic thrombocytopenic purpura, anti-factor VIII antibodies in hemophilic patients, autoantibodies against endothelial cells in thrombotic thrombocytopenic purpura/hemolytic uremic syndrome as well as in neurological disorders (myasthenia and Guillain-Barre syndrome) [48].

Although most of the reports regarding the use of immunoadsorption are non-controlled studies performed in small groups of patients, now some results from prospective randomized trials are also available. Such studies were performed mainly in rheumatoid arthritis patients. Furst and colleagues compared the results of treatment with sham procedure (apheresis only, with blood circulating through a by-pass loop around the column to ensure blindness) and staphylococcal protein A immunoadsorption in patients with severe rheumatoid arthritis. The significant improvement in clinical symptoms was found in 41.7% of IA patients who completed the whole course of therapy versus 15.6% of those on sham treatment. The duration of response after the full course of treatment was very long and lasted 37 +/- 5.3 weeks [49].

Side effects of LDL-apheresis and immunoadsorption

Side effects of LDL-apheresis and immunoadsorption, although significantly less pronounced in comparison to 'classical' PE are still very important. They may be related to several factors. First, they may be related to the extracorporeal circuit, central venous access, plasma separation procedures or anticoagulation; all these conditions are relatively 'universal' for most of extracorporeal blood purification techniques. More specific adverse effects of LDL- apheresis and IA are related to the contact between plasma and the ligand used. In this respect the staphylococcal protein A deserves special attention. The basic biological role of this agent (being the part of bacterial cellular wall) is to activate immune system and stimulate cytokine release. In addition, depending on technology, SPA may be contaminated with other agents, such as enterotoxins [31,48]. Hence, the treatment with IA may be complicated by allergic reactions and the prophylactic use anti-histaminic drug prior to the procedure is highly advisable. These reactions may be mild and transient, mostly limited to skin (urticaria), but also more generalized, for example resulting in hypotension, joint pains and swelling, fever and even convulsions. Relatively rare complication that may occur in patients treated with IA using staphylococcal protein A columns is small vessel vasculitis related to the development of SPA/SPA-antibody immune complexes [50].

There is an extremely interesting study that focused on possible side effects of IA using double blind, randomized approach, performed in rheumatoid arthritis patients and comparing IA with sham treatment. In this study all patients and study personnel were blinded against the treatment used, and the preparation of the extracorporeal circuit was exactly the same. The only difference between the treatment groups was the by-pass of plasma around the IA column in sham-treated patients. Interestingly, the incidence of adverse reactions was equal in both groups and thus – related probably to extracorporeal circuit itself and/or to plasma separation [49].

As in the case of PE, the series of IA procedures may also lead to systemic immunoglobulin depletion and further immunosuppressive state; hence it may be complicated with serious systemic infections [27]. Albumin deficiency may also occur after few procedures [31].

In the opinion of the authors of this review special attention should be paid on hypotension occurring during LDL-apheresis and immunoadsorption. It must be kept in mind that blood pressure lowering in dextran-sulphate columns may be attributed to enhanced bradykinin release, since prekallikrein becomes activated on the contact with this polyanionic membrane. Hence, it is important to remember that treatment with ACE inhibitors should be discontinued prior to the initiation of IA treatment. The unintentional administration of mentioned drugs may result in severe hypotension and 'anaphylactoid' reactions [3,4]. This seems to be the issue of superior importance since the renin-angiotensin-aldosteron system blockade is currently the most important strategy for amelioration of proteinuria and renal failure progression, with an excellent support form a number of prospective and randomized studies. Many of patients being candidates for LDL-apheresis/IA would additionally benefit from the concomitant use need of these renoprotective of cardioprotective drugs and deprivation of this treatment would be very problematic. However, in these cases switching from ACEi to ATII receptor blocking agent is probably safe [1,3].

Future considerations

Reviewing the literature regarding the issue of LDL--apheresis and immunoadsorption we have a strong impression, that these methods are the milestones in the treatment of many autoimmune diseases since the introduction of steroids and cyclophosphamide as immunosuppressive agents. In our opinion encouraging results of many clinical trials should change the use of this method not only as a rescue therapy for patients who do not respond to other conventional treatment. We believe that these techniques should be employed earlier, possibly even as a first-line therapy in patients who display the risk factors for poor prognosis and fast progression of the disease as well as in those with contraindications for 'classical' immunosupression. We also think, that despite the fact that LDL-apheresis and IA are very expensive, their early use in well-selected cases may also

benefit from financial point of view. An early response to this treatment may significantly reduce the costs of hospitalization, cease unsuccessful immunosupression, limit its complications and possibly reduce overall costs postponing renal replacement therapies.

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