LDL-apheresis and immunoadsorption: novel methods in the treatment of renal diseases refractory to conventional therapy

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Abstract
Plasma exchange was used for many years as the method of extracorporeal removal of antibodies and/or immune complexes that may be involved in the pathogenesis of renal diseases. Recently low-density lipoprotein (LDL)-apheresis and immunoadsorption were also introduced into nephrological practice. LDL-apheresis, designed originally as a rescue treatment for refractory hyperlipidaemia, appeared also to be effective in certain glomerulopathies, resistant to other treatment strategies. Similarly, immunoadsorption can be employed successfully in the treatment of different nephropathies, of both immunological and non-immunological pathogenesis. This method may also be effective as rescue treatment in some cases of acute rejection and recurrence of certain nephropathies after renal transplantation. The major advantage of both methods is their increased selectivity compared with standard plasma exchange. In addition, these techniques need no supplement fluid (namely fresh frozen plasma), which allows for markedly increased efficacy of the treatment as well as substantial reduction of infection risks.

Keywords: focal segmental glomerulosclerosis; immunoadsorption; LDL-apheresis; lupus nephritis; plasmapheresis; refractory nephrotic syndrome

Introduction
Plasma exchange (plasmapheresis, PE) is one of the techniques of extracorporeal blood purification used not only for the treatment of kidney diseases, but also for many other indications in the neurological and toxicological fields. This method appears to be highly effective in certain diseases (e.g. anti-glomerular basement membrane glomerulonephritis, haemolytic-uraemic syndrome, recurrence of certain glomerulopathies in transplanted kidney), whereas in others its effectiveness remains doubtful and lacks good support by prospective clinical trials. Although relatively safe, this method still carries some risk for the patient, both acute (related to the procedure itself) and delayed, such as the risk for transmission of certain viral infections with the fresh frozen plasma used as the supplement fluid. Unfortunately, during therapeutic elimination of immunoglobulins or immune complexes, this method poses the risk related to non-selective, uncontrolled elimination of other circulating agents, including blood coagulation factors, hormones, etc. Thus, the efforts of researchers are aimed at the development of new techniques that might provide more selective treatments, targeting certain circulating pathogenic agents without the undesired removal of physiological factors.

Among novel methods used in extracorporeal blood purification, two of them attract the special attention of the nephrologist: low-density lipoprotein (LDL)-apheresis and immunoadsorption (IA). Selectivity and safety superior to PE characterize both these methods.

LDL-apheresis in kidney diseases

Although the initial concept of LDL-apheresis was to lower LDL-cholesterol in refractory (familial) hypercholesterolaemia, this method appeared to be very effective in the treatment of nephrotic syndrome (NS). The employment 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 by its influence on the course of different nephropathies.
There are only a few indications in which the usefulness of LDL-apheresis in renal patients seems to be proven, although mostly by non-randomized observations performed in small sample size populations. These include primary focal glomerulosclerosis (FGS), recurrence of FGS in transplanted kidney, and lupus nephritis. Anecdotal reports indicate that many other glomerular diseases might be treated successfully with LDL-apheresis, when other therapies appear ineffective.

Yokoyama and co-workers showed a significant decrease of daily protein loss and increase in glomerular filtration rate (GFR) after a course of LDL-apheresis in 14 patients with FGS refractory to previous treatment [1]. Six procedures performed over 3 weeks were sufficient to achieve the improvement in GFR, reduction of daily protein loss and normalization of lipid profile for more than 6 months of follow-up. Interestingly, repeated biopsies performed 3 months after LDL-apheresis therapy revealed the regression of histopathological lesions when compared with the initial specimens. The response to treatment was better in patients with less severe sclerosis on the initial biopsy, but—interestingly—also in those presenting with a more severe nephrotic syndrome at commencement of treatment [1]. Many case reports confirm that LDL-apheresis may be employed successfully in the treatment of FGS and that along with a lowering of the serum lipid profile, proteinuria decreases, serum total protein and albumin levels increase and renal function improves [2]. The concomitant use of HMG-CoA inhibitors may additionally enhance the effect of LDL-apheresis [3]. Use of the mentioned drugs is also advisable to avoid a rebound effect (i.e. the return of serum lipids to pre-treatment level after withdrawal of the procedure).

The use of LDL-apheresis in lupus nephritis should probably be restricted to those cases resistant to other therapies, especially when other, non-renal, involvement is present. Daimon and co-workers described such a patient with rapidly progressing glomerulonephritis in the course of systemic lupus, with the presence of crescents in 11 out of 22 glomeruli in a renal biopsy specimen, and who needed dialysis due to rapid deterioration of renal function [4]. The initial use of plasmapheresis was sufficient to recover renal function and stop renal replacement therapy, although it did not protect the patient from severe NS. This state was treated further with LDL-apheresis using Liposorba columns and later on with DNA adsorption using Selesorb columns. This case report provides an excellent example of an ‘integrated’ extracorporeal treatment using four (including haemodialysis) blood purification techniques for treatment of severe systemic lupus.

LDL-apheresis also proved its usefulness in other diseases associated with NS resistant to immunosuppressive therapy, such as minimal change nephritis [5]. Interestingly, LDL-apheresis may also ameliorate renal function in diabetic nephropathy [6].

**Immunoadsorption in kidney diseases**

IA allows for selective elimination of immunoglobulins and other circulating agents that might be involved in the pathogenesis of different diseases, mostly of immunological (autoimmune) origin. This selectivity is largely dependent on the type of membrane and especially on the type of ligand used for adsorption. These agents include staphylococcal protein A (SPA), tryptophan, phenylalanine, monoclonal sheep anti-IgG human immunoglobulin and dextran sulfate [7–11]. IA selectivity may be increased further using more specific ligands, such as anti-β2-microglobulin antibody-containing columns designed exclusively to eliminate β2-microglobulin in dialysis patients [10–13]. IA using specific LDL (apolipoprotein B)-binding antibodies or dextran sulfate is also used for LDL-cholesterol elimination, as was discussed above.

The need for selective extracorporeal antibody elimination is especially important in rapidly progressing, refractory nephropathies with poor renal prognosis. This is especially true for rapidly progressive glomerulonephritis. In the early report of Palmer et al., the authors described significant improvement of renal function in 10 patients with crescentic glomerulonephritis already on dialysis [14]. In all cases, IA coupled with continuous immunosuppression resulted in recovery of renal function and independence from dialysis, accompanied by resolution of glomerular crescents.

Another important group of diseases that may manifest as crescentic glomerulonephritides are anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitides. Mátic and colleagues reported three cases of Wegener’s granulomatosis with severe renal and other systemic involvement successfully treated with IA (although without full recovery of renal function in two of the three cases). In all patients, the clinical improvement was accompanied by complete elimination of c-ANCA antibodies [7].

PE is not effective in the treatment of systemic lupus erythematosus (SLE). IA appeared to be useful in the treatment of severe cases of SLE, probably because it allows much larger volumes of plasma to be treated. Although prospective studies are lacking, preliminary clinical reports are very promising. Suzuki et al. [15] 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 a mean number of 3.7 IA procedures using dextran sulfate as a ligand. The use of IA together with steroids and/or cyclophosphamide allowed for a significant reduction of total dose of immunosuppressive agents [15].

Another important advantage of the IA technique in SLE is its effectiveness in the elimination of anti-cardiolipin antibodies. The onset of antiphospholipid syndrome leads to very serious complications and
increased mortality among patients, mainly due to thrombosis and recurrent abortions in pregnant women with SLE. Hence, the new alternative for treatment of this disease may be of great importance [16].

In 1999, Esnault et al. presented the results of treatment with IA in nephrotic syndrome of different aetologies. They used repeated IA to protein A columns in nine patients with primary (membranous glomerulonephritis, IgA glomerulonephritis) and secondary (amyloidosis, diabetic nephropathy) renal diseases. A significant reduction of proteinuria from a mean of 12.6 ± 5.49 to 3.35 ± 2.2 g/24 h (75.4% decrease) was achieved. The most interesting observation in that study was that the authors obtained significant amelioration of proteinuria also in a non-immunologically mediated disease, i.e. diabetic nephropathy [17].

**Immunoadsorption in kidney transplantation**

The usefulness of the discussed method was also shown in renal transplantation. Haas and colleagues used IA to lower the level of panel-reactive antibodies (PRAs) in patients awaiting re-transplantation. They performed up to 24 sessions in the pre- and early post-transplant period in 20 highly sensitized patients (median PRA 87%), achieving excellent patient and graft survival [18]. Boehmig et al. treated acute humoral renal transplant rejection in 10 patients displaying C4d deposits in peritubular capillaries on renal biopsy, using IA onto protein A (the median number of sessions equalled nine), together with standard anti-rejection therapy. In eight out of 10 treated patients, prolonged normalization of graft function was achieved for a mean period of 14.2 ± 7.1 months [19].

IA is thought to be effective in the treatment of recurrent FSG after renal transplantation. Büssemaeker et al. described a patient with severe NS (urinary protein loss of up to 35 g/day, with advanced glomerular lesions on graft biopsy 7 months after transplantation), in which IA to tryptophan (11 consecutive sessions) was able to reduce the proteinuria to 2.0 g/day, restore serum albumin level and normalize renal function [9]. Other authors also reported a successful outcome in recurrent FSG in renal transplant recipients treated with IA [20,21]. Belson et al. described a 9-year-old patient who started plasmapheresis on the twelfth day post-transplant because of severe NS due to recurrent FGS, followed by immunoadsorption on a protein A column from the eighth month post-transplant, and remained on this treatment for up to 60 months [22].

**Side effects of LDL-apheresis and immunoadsorption**

The side effects of LDL-apheresis and IA may be related to the extracorporeal circuit, central venous access, plasma separation procedures, anti-coagulation, or, to contact between plasma and the ligand used. From this point of view, special attention was focused on the staphylococcal protein A (SAP). The main biological role of this agent (originating from the bacterial cell wall) is to activate the immune system and stimulate cytokine release. In addition, depending on technology, SPA may be contaminated by other agents, such as enterotoxins [17,23]. Hence, the treatment with IA may be complicated by allergic reactions (an antihistamine drug as a prophylaxis is advisable prior to the procedure), hypotension, convulsions, joint pains and fever. The series of IA procedures may also lead to systemic immunoglobulin depletion and further to an immunosuppressive state; hence it may be complicated by serious systemic infections [5]. Albumin deficiency may also occur after a few procedures [17].

Hypotension occurring during LDL-apheresis and IA may be a serious complication of these procedures. Hypotension during procedures utilizing dextran sulfate columns may be attributed to enhanced bradykinin release, since pre-kallikrein becomes activated on contact with this polyanionic membrane. Hence, it is important to remember that treatment with angiotensin-converting enzyme (ACE) inhibitors must not be used during the course of IA. These drugs, administered by mistake may lead to severe hypotension and an ‘anaphylactoid’ reaction [24,25]. This contra-indication may be of clinical significance, since many patients treated with LDL-apheresis (i.e. patients with chronic nephropathies or heart failure) would benefit additionally from the concomitant use of these renoprotective and cardioprotective agents.

**Future considerations**

In our opinion, the encouraging results of many clinical trials should influence the current policy of employing the methods discussed. Possibly they should be used not only as rescue therapies for patients who do not respond to other conventional treatment, but also as first-line therapy in patients who display risk factors of poor prognosis and/or dynamic disease progression, and in those with contraindications for ‘classical’ immunosuppression. We also think that, despite the fact that LDL-apheresis and IA are very expensive, their early use in well-selected patients may also prove to be financially very beneficial. An early response to this treatment may substantially reduce costs of hospitalization, exposure to unsuccessful immunosuppression together with its complications, and possibly, renal replacement therapy.

**References**


