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Extracorporeal Therapies in the Treatment of Focal Segmental Glomerulosclerosis

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Abstract
Focal segmental glomerulosclerosis (FSGS) is one of the most frequent and severe glomerular kidney disease with frequent progression to end-stage renal disease and a high rate of recurrence in renal transplantations. Due to intolerance or resistance to the current immunomodulatory treatments, the management of FSGS is a therapeutic challenge. Over the last few years, development in extracorporeal therapies has shown potential beneficial outcomes in drug-resistant and recurrent FSGS patients. Thus, this study reviews the current literature on the use of extracorporeal therapies, such as plasma exchange therapy, immunoadsorption, and low-density lipoprotein apheresis, for the treatment of FSGS in the pediatric population.

Introduction

Focal segmental glomerulosclerosis (FSGS) is one of the leading causes of nephrotic syndrome (NS) in both pediatrics and adults [1]. In pediatrics, FSGS known to comprises 7–15% [2]. Throughout the last 20 years, there has been a steady increase in the incidence of FSGS, most likely due to increase in patients progressing to end-stage renal disease (ESRD). Although, the progression of FSGS to ESRD, most commonly in FSGS patients, is resistant to steroid and immunosuppressive drugs [3, 4]. Of those patients that undergo renal transplantation, it has been reported that up to 56% of patients will have a recurrence of FSGS (rFSGS) in the transplanted kidney [1, 5]. The standard of care for treatment of FSGS commonly involves corticosteroid and immunosuppressive therapy; however, these treatments have shown to have a limited response in resistant patients and those with rFSGS. Therefore, we focus here on the use of extracorporeal therapies for the management of FSGS, especially within the pediatric population.

Classification and Pathophysiology

FSGS is a histological pattern of glomerular lesion defined by both clinical and pathologic findings. FSGS is either classified as primary (idiopathic) or as secondary due to a wide array of causes, such as illicit drug use, HIV, or other viral infections [6]. Primary FSGS (pFSGS) is currently the most common cause of ESRD in the United States (US) and has shown to occur most commonly in children and young adults. Additionally, FSGS

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can recur after kidney transplantation, and a recurrence rate of 20–50% has been reported with half of the patients suffering from graft loss [7]. Recurrent FSGS manifests in one of 2 ways: early versus late recurrence. Early recurrence is normally characterized by massive proteinuria within hours to days after transplantation, whereas late recurrence develops several months or year after transplantation [7]. Clinically, FSGS presents with a triad of findings: nephrotic range proteinuria (proteinuria >50 mg/kg/day), low serum albumin (<2.5 g/dL), and edema [4]. The pathophysiology behind FSGS is still being fully elucidated, but there have been great strides over the past several decades. Genetic causes have been found in some patients with FSGS [4]. These genetic causes include various mutations affecting structural, mitochondrial, nuclear, and other intracellular proteins [4]. While there are genetic etiologies for FSGS, the majority of patients likely have a nongenetic cause. One of the main nongenetic causes is podocyte injury and loss, which leads to foot process effacement and glomerulosclerosis. Electron microscopy of the kidney typically reveals the effacement of podocytes with progression to FSGS [3]. The major causes of podocyte damage include the alteration or impaired formation of the slit diaphragm complex, alteration of the glomerular basement membrane or its interactions with the podocyte, the alteration of the apical membrane domain of the podocyte, and the existence of a circulating factor or factors [3, 4, 7].

The Mystery of Circulating Permeability Factors

Although the pathophysiology of pFSGS is still unknown, it is hypothesized that circulating permeability factors cause progressive podocyte injury leading to both pFSGS and rFSGS [8]. This was detected when the serum of rFSGS patients induced FSGS within rat models [9, 10]. Additionally, in a study by Zimmerman et al. [10], the effluent from the immunoadsorption (IAS) columns used for the treatment of rFSGS patients was injected into rat models. This led to a 3–4.6-fold increase in urinary albumin excretion in these animals [10]. After further investigation of the transplant serum, a potential candidate for the permeability factor was identified as a plasma protein with a molecular weight of approximately 50 kDa, which is sensitive to heat and protease treatment. Wei et al. [11] further identified serum soluble urokinase receptor (suPAR) as the possible candidate. In their study, the authors showed that chronic suPAR administration or overexpression in uPAR mice caused foot process effacement followed by glomerulopathy and proteinuria [11]. Another study by Wei et al. [12] further confirmed abnormally high levels of suPAR in FSGS patients than in patients with other glomerulopathies. However, additional studies are required as uncertainty still persists. Other potential candidate factors, such as vasodilator-stimulated phosphoprotein, apolipoprotein A-I, galactose and cardiotrophin-like cytokine-1 have also been proposed but further studies are needed to further justify [6].

Potential of Extracorporeal Therapy for Treatment of FSGS

The mainstay treatment for FSGS focuses on the normalization of proteinuria while preventing and decreasing the rate of progression to ESRD [13]. Corticosteroids are usually the first line of treatment due to their efficacy in inducing remission of proteinuria in FSGS patients. However, steroid therapy has a limited remission rate of 20–50% and accompanied by severe side effects, such as growth impairment, hypertension, and immune suppression [13, 14]. Additionally, patients can become steroid-resistant or dependent and many of these patients have shown to develop ESRD. Cyclophosphamide or calcineurin inhibitors, such as tacrolimus and cyclosporine A (CsA) in conjunction with prednisolone, are indicated for the treatment of steroid resistant or steroid intolerant FSGS patients. Although, response rates for these treatments are very low (<25%) and accompanied by significant complications [13, 15]. Renal transplantation has also been used for the treatment of FSGS, however, FSGS has shown to recur in 30–40% of patients [16]. Recurrence in the transplanted kidney can occur as quickly as hours after transplant or several years following. Furthermore, FSGS recurrence is the leading cause of graft failure in children and has the lowest 5-year graft survival rate for living donor renal transplant recipients compared to other renal disorders [16]. Despite all the treatment options, FSGS can still lead to ESRD and management remains a major challenge. Though, various literature on extracorporeal therapies have highlighted its efficacy and potential benefits in the treatment of steroid-resistant or recurrent FSGS. The involvement of a circulating factor or factors in FSGS has led to the use of various extracorporeal systems for treatment, such as plasma exchange (PE), IAS, and low-density lipoprotein-apheresis (LDL-A) therapy.

Table 1. PE and IAS for rFSGS in the pediatric population

Study	Number	Patient characteristics	Therapy	Outcome
Cochat et al. [21], 1993	3	3 female – age 6.5–15.8 years	PE followed by methylprednisolone pulses and CPM over 2 months	All patients had complete remission after an 18–27-month follow-up
Mowry et al. [19], 1993	11	N/A	PE + high dose CSA	Complete remission in 7 patients, partial remission in 3. Two patients lost graft
Kawaguchi et al. [22], 1994	5	N/A	PE	Complete remission in 4/5 patients
Laufer et al. [23], 1998	2	2 male – age 11 and 13 years	PE	Complete remission in both patients
Dall'Amico et al. [20], 1999	11	Age 2–14 years	PE + 2 month course of CPM	Proteinuria reversal in 9/11 patients, perstistent remission in 7/11 after 32 ± 15 months, temporary remission in 2/11
Cheong et al. [24], 2000	6	4 male, 2 female – mean 7.2 ± 3.3 years	PE + CPM	Complete remission in 3 patients, parital remission in 3 patients
Saleem et al. [25], 2000	3	1 male, 2 female – age 2–13 years	PE with methylprednisolone and CPM	All patients had improvement in renal function and reduction of proteinuria
Pradhan et al. [26] 2003	4	2 male, 2 female – age 1–14 years	PE	All 4 patients went into remision with good graft function
Haffner et al. [27], 2005	1	Male – 10 years	PE + high dose CSA and CPM	Complete and sustained remission with stable renal function after 28 months of treatment
Fencl et al. [30], 2007	2	2 female, age 16 and 13 years	35 PE + 38 IAS procedures; 39 PE + 16 IA procedures	One patient had partial remission while the other had complete remission
Allard et al. [31], 2018	12	6 male, 6 female – age 2–13 years	IAS (median of 4.2 sessions during 1st week and 2.5 sessions during second week)	Complete remission in 8/12 patients, Partial remission in 2/12 patients with no graft loss

PE, plasma exchange therapy; IAS, immunoadsorption; rFSGS, recurrence of focal segmental glomerulosclerosis; CPM, cyclophosphomide; CSA, cyclosporine A.

Non-Specific Treatment via PE Therapy

Of the various extracorporeal treatments, PE therapy is the most widely studied as well as the most adopted intervention [17]. PE therapy has been postulated to rapidly remove the circulating permeability factor leading to improvement in proteinuria and renal function. Remission rates have shown to vary based on the literature but a review by Ponticelli et al. [18] reported a remission rate of approximately 70% in children. While controlled studies are largely unavailable, there is a plethora of case reports and case series regarding its utility in rFSGS (Table 1) [19–27]. It is important to note that PE in all reported cases was used in conjunction with immunosuppressive therapy, notably steroids, cyclophosphamide, and CsA.

In a study by Mowry et al. [19], 11 children with rFSGS were treated with high-dose CsA with 10–12 sessions of PE therapy. As a result, there was a reduction in the urinary protein creatinine ratio (61 ± 44 to 2.8 ± 33) and this led to complete remission in 7 patients and partial remission in 3 patients after a follow-up of 28 ± 21 months. Similarly, a study by Dall'Amico et al. [20] studied 29 children with pFSGS. rFSGS occurred in 11 children who tested positive for the permeability factor and 9 of them were treated with PE and cyclophosphamide. The investigators reported that 7 patients had achieved persistent remission after 32 ± 15 months with a total reversal of proteinuria in all 9 patients. Despite the lack of controlled studies, given the outcomes reported, PE was included in the kidney disease: improving global outcomes guidelines for the treatment of post-transplant rFSGS in 2009 [28].

Semi-Selective Treatment via IAS

IAS is a semi-selective system that is starting to gain traction in the treatment of FSGS. IAS is a modification of PE in which circulating factors are selectively removed from the separated plasma with the help of specific ligands in high-affinity absorption columns [29]. These IAS systems include the Immunosorba® and Globaffin®

columns from Fresenius Medical Care. Immunosorba® contains protein A from the cell wall of *Staphylococcus aureus* and has a high affinity for immunoglobulin G (IgG) antibodies. Similarly, Globaffin® contains a synthetic peptide, GAM, which also has a high affinity for antibodies, primarily IgG [29]. Another IAS system is the TheraSorb® by Miltenyl Biotec and it can remove varying types of immunoglobulin antibodies, such as IgG, IgA, IgM, IgE, and various immune complexes.

There are several case series and reports regarding the use of these systems within adults, however, the pediatric literature is quite scarce (Table 1) [30, 31]. In a retrospective study from 2011 to 2014, Allard et al. [31] studied 12 children with rFSGS following kidney transplantation. In this population, both Immunosorba® and Therasorb® were used. Of the 12 patients, a total of 10 responded with 8 having complete remission and 2 achieving partial remission. Following initial remission, only 2 were able to maintain remission without repeated IAS, whereas, the other 8 became IAS dependent. Additionally, IAS was also performed on 2 patients that were resistant to PE therapy and neither of them showed any response [31]. Through this study, IAS has shown to be beneficial as a treatment; though, larger studies with a prospective, randomized design are further needed.

Selective Treatment via Lipoprotein Apheresis

LDL-A is the primary selective extracorporeal system that has been reported and studied in its use in FSGS. LDL-A has shown to induce remission of proteinuria with recovery from FSGS and also improves the response rate to steroid and immunosuppressive therapy. Although the mechanism by which LDL-A induces these beneficial outcomes is poorly understood, several theories have been postulated [32]. As a result of reduced LDL levels, there is recovery of macrophage function due to the lipotoxic effect on glomeruli/interstitium and better response to steroid and immunosuppressive therapy due to improved intracellular drug transport. LDL-A has also shown improvement in endothelial dysfunction possibly due to the decreased vascular cell adhesion molecule-1 levels and better blood flow due to the removal of fibrinogen and other anticoagulants [32]. Additionally, LDL-A has also shown reduced levels of vascular permeability factor and provides anti-inflammatory effects due to reduced levels of LDL oxidation, C-reactive protein, intercellular adhesion molecule-1, and P-selectin [32]. Currently, LDL-A is commonly performed using the Food and Drug Administration (FDA) approved Liposorber® LA-15 system.

Liposorber® LA-15 System

In the original iteration of LDL-A by Lupien et al. [33], the technique utilized heparin-agarose beads within blood pack units to which the patient's blood was added. This was repeated 7–8 times resulting in LDL and very-LDL (VLDL) being selectively bound to the heparin-agarose and being filtered out prior to transfusion back to the patient. Stoffel et al. [34] modified the procedure in 1981 to be selective for LDL. This process utilized anti-LDL sepharose, an agarose bead immunoadsorbent. Two glass columns were utilized to separate out LDL prior to blood return to the patient, and this technique was coined as LDL-A [34].

Since Stoffel et al. [34] introduced this technique; several subsequent methods have been developed including IAS, dextran sulfate cellulose adsorption, heparin extracorporeal LDL precipitation, and direct adsorption of lipoprotein using hemoperfusion (Table 2). All of which have been applied for the management of familial hypercholesterolemia, while only dextran sulfate cellulose adsorption has being applied to drug-resistant NS [35].

Dextran sulfate cellulose adsorption is a technique, which relies on negatively charged dextran sulfate bound to cellulose beads. Both LDL and VLDL are separated from heparinized plasma via negatively charged dextran sulfate bound to cellulose beads. This can result in a 76–81% decrease in LDL as well as a 65–68% decrease in lipoprotein (a) levels [35].

The Liposorber® LA-15 system relies on this dextran sulfate cellulose adsorption method and is composed primarily of 3 single-use disposable parts. This includes 2 adsorption columns containing 150 mL each of dextran sulfate cellulose and a Sulflux KP-05 plasma separator containing ethylene-vinyl alcohol copolymer-coated polyethylene hollow fibers [36]. These are connected via NK-M3R(U) tubing system for plasmapheresis and a MA-03 apheresis unit for control of the LDL-A [36].

The system works by withdrawing blood from the patient via the NK-M3R(U) tubing and combined with heparin to prevent clotting and significant volume loss. It then flows into a Sulflux KP-05 plasma separator where plasma is separated from the cellular components [35, 36]. Afterward, the separated plasma is delivered to the LDL absorption column where 2 dextran sulfate cellulose filters absorb and remove LDL, VLDL, and lipoprotein (a) from the plasma. Here, 2 adsorption columns are used to provide continuous apheresis. When 1 column is exhausted, the system continues to perform apheresis via the second column while the first column

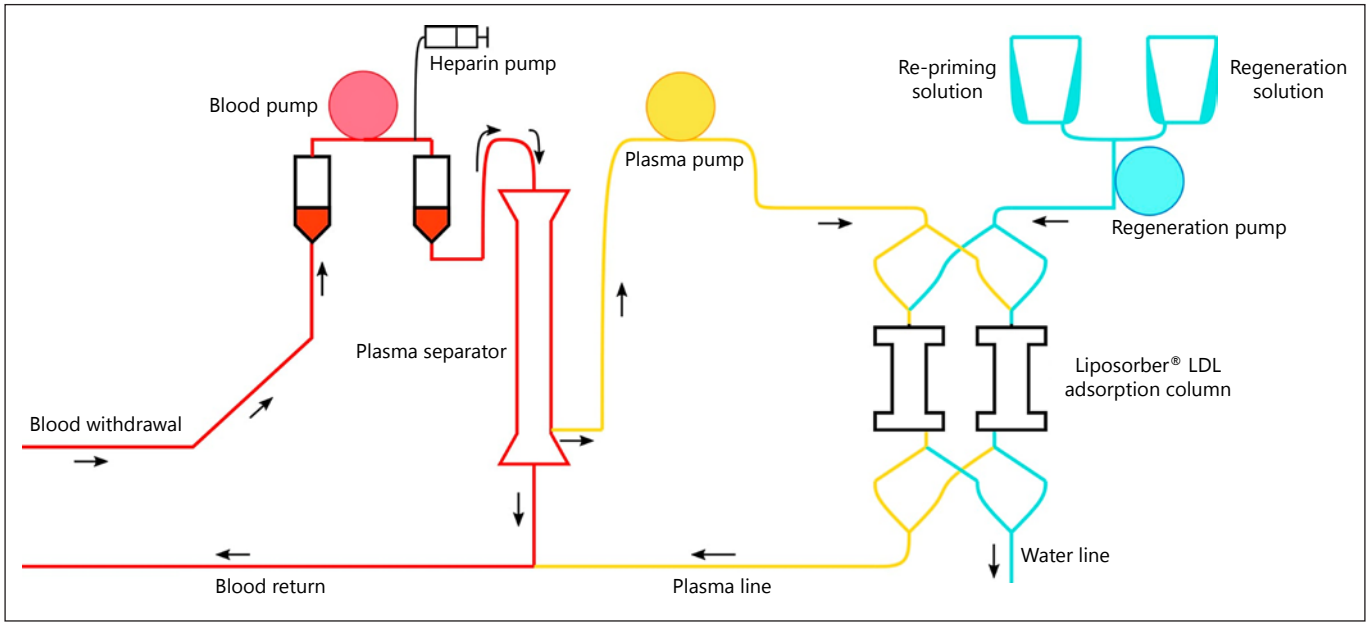

Fig. 1. Outline of the Liposorber® LA-15 system. LDL, low-density lipoprotein.

Table 2. Comparison of different LDL-A techniques

Technique	Description and application	Lipids removed (%)
IAS	Selective LDL removal through anti-LDL antibody (polyclonal sheep antibodies to human apoB_{100}). Glycine buffer used for column regeneration. Used mainly for management of FH	Each session removes up to 55% of LDL and Lp (a)
Dextran sulfate cellulose adsorption	Removal of both LDL and VLDL using negatively charged dextran sulfate covalently bounded to cellulose beads. Five percent sodium chloride is used to regenerate the columns. Widely used for managment of drug-resistant NS and FH	Decrease in Lp (a) levels by 65–68% and LDL levels by 76–81%
HELP	Removal of LDL via precipitation. Plasma is treated with low pH (4.85) heparin and precipitated LDL is removed by filtration. Used mainly for management of FH and also reduces hepatitis C RNA and CRP level	Decrease in Lp (a) by 62%, LDL by 50%, and fibrinogen levels by 50%
DALI using hemoperfusion	Removal of LDL and La (a) using negatively charged polyacrylate-coated polyacrylamide absorber. Used mainly for management of FH	Decrease in LDL and Lp (a) levels by 40–45%

LDL-A, low-density lipoprotein-apheresis; IAS, immunoadsorption; FH, familial hypercholestrolemia; Lp (a), lipoprotein (a); NS, nephrotic syndrome; VLDL, very low-density lipoprotein; HELP, heparin extracorporeal LDL precipitation; DALI, direct absorption of lipoprotien; CRP, C-reactive protein.

is regenerated. The switch from one column to the other is regulated by a computer program and occurs automatically [36]. Next, the filtered plasma is flushed with Ringer's lactate (replacement solution) and 5% sodium chloride. Afterward, the plasma is passed through a membrane filter, reunited with the cellular components of the blood and returned to the patient (Fig. 1). The standard prescription and protocol for LDL-A with the Liposorber® LA-15 system are shown in Table 3 [36]. The reported sided effects have varied, but it includes a 10, 2–2.5, 0.3–2.5, 0.06, and 0.2–0.3% incidence of infection of the vascular access device, hypotension, nausea and vomiting, allergic reactions, and anginal pain, respectively [37, 38].

Table 3. Liposorber LA-15 prescription

Performed 2–3× a week for 4 weeks then 1× a week for 6 weeks
Plasma volume (mL) to be treated = Patient weight (kg) × 60 (round to the nearest hundreth)
Heparin anticoagulation – Priming solution: 2,000–3,000 USP units of heparin in 1 L Ringer's lactate – Loading dose: heparin 25 USP units/kg (reduced if abnormal PT/PTT) – Continuous infusion: heparin 25 USP units/kg/h – Monitor PT, PTT, ACT – ACT should be 1.5–3× normal range – Typically, 1,000–3,000 USP units of heparin/h is adequate

ACT, activated clotting time; PT, prothrombin time; PTT, partial thromboplastin time.

FDA Approval and Humanitarian Device Exemption

As of currently, 2 LDL-A systems have been approved by the US FDA. The Liposorber® LA-15 system (Kaneka Pharma, New York, NY, USA) was first approved by the FDA through the premarket approval process in February 1996 [36, 38]. It was approved specifically to remove serum LDL from high-risk patients for whom management via diet had been ineffective or not tolerated. Furthermore, the Liposorber® LA-15 system was approved for a Humanitarian Device Exemption in October 2013 for use in the treatment of pediatric patients with drug-refractory pFSGS in both native (GFR ≥60 mL/min/1.73 m^2) as well as post-transplant kidneys [38, 39]. Similarly, the HELP System (B. Braun, Melsungen, Germany), which utilizes heparin-induced extracorporeal LDL precipitation, received approval by the FDA in September 2007 through the premarket approval process [39].

Evidence of Efficacy LDL Apheresis for FSGS in the Pediatric Population

The treatment of FSGS in children using LDL-A has not been widely studied due to the limited published studies and case reports. Therefore, several studies in this review include both the adult and pediatric population. In one retrospective study of 11 children with pFSGS resistant to CsA and steroids, Hattori et al. [40] investigated and compared the effect of LDL-A combined with and without prednisolone therapy. A total of 12 LDL-A sessions were provided twice a week for 3 weeks followed by 6 weeks of once a week sessions with daily prednisolone (1 mg/kg). In patients undergoing LDL-A monotherapy, the authors reported a significant change in total cholesterol and triglycerides with no significant difference in LDL and proteinuria levels [40]. However, with the combined treatment, an efficacy rate of 76% was reported as 5 patients had achieved complete remission and 2 had attained partial remission. This suggests that LDL-A alone was not able to induce remission. Additionally, 1 of the 2 children who had partial remission achieved stable renal function at 4.5 years follow-up while the other patient gradually developed ESRD, similar to the other 4 non-responding patients [40]. In another prospective study by Muso et al. [41], 17 steroid-resistant patients with FSGS and minimal change NS (MCNS) were treated with LDL-A and a full dose of steroids. This study also included a control group of 10 FSGS and MSCN patients, resistant to steroids. The control group was solely treated with full-dose steroids. LDL-A therapy was provided twice a week for 3 weeks and then weekly for 6 weeks for a total of 12 sessions [41]. Within 9 weeks of treatment, the combined group showed a significant reduction in proteinuria in comparison to the control group. Overall, there was a 76% efficacy rate as 9 patients achieved complete remission, while 4 patients attained partial remission [41]. In a prospective study of 5 individuals with drug-resistant FSGS, Tojo et al. [42] studied combination therapy of LDL-A and double-filtration plasmapheresis. The combined treatment consisted of 6–8 alternating cycles of LDL-A and double-filtration plasmapheresis. Overall, there was a decrease in proteinuria, improvement in blood flow, and 1 patient achieved partial remission [42]. In a different study, Muso et al. [43] studied 8 patients with steroid-resistant FSGS or MCNS. All patients were treated with a combination of LDL-A and steroid pulse therapies. The number of sessions, duration, and interval time between the sessions varied for each patient. Throughout the study, 5 patients responded to treatment and showed significant improvement in hyperlipidemia, a decrease in proteinuria (<3.5 g/day), and an increase in serum albumin levels [43]. All 5 of those patients attained complete remission. Out of the other 4 patients, 1 patient had partial remission, while the other 3 became resistant to treatment [43]. Several additional studies have illustrated similar beneficial effects (Table 4) [1, 35, 40–45].

Role of LDL Apheresis in Potential Cardiovascular Benefit in FSGS

LDL-A may also have potential cardiovascular benefits in addition to the positive renal outcomes in the treatment of FSGS. A currently ongoing clinical study by Kaneka Pharma America LLC is investigating whether removal of lipoprotein-associated PLA2 (Lp-PLA2) and lipid metabolites through LDL-A lead to the improve-

Table 4. Studies of LDL-A for FSGS in pediatric patients

Study	Number	Age, years	Primary disease	LDL-A technique	Apheresis treatment	Outcome
Hattori et al. [40], 2003, retrospective	11	7–14.4 (10.9 ± 2.7)	FSGS (resistant to steroids, CPM and CSA)	Dextran sulfate cellulose adsorption	6 sessions (2× week for 3 weeks) followed by 1× week for 6 weeks. Total of 12 sessions	CR: 5 patients, PR: 2 patients. Efficacy rate of 76%. Effective in PSL resistant patients
Muso et al. [41], 2001, prospective	17	15–65	FSGS (14) or MCNS (3) (resistant to steroids)	Dextran sulfate cellulose adsorption	6 sessions (2× week for 3 weeks) followed by 1× week for 6 weeks. Total of 12 sessions	CR: 9 patients, PR: 4 patients and no effect in 4 patients. Efficacy rate of 76%
Yokoyama et al. [44], 1998, retrospective	14	N/A	FSGS (resistant to steroids)	N/A	Total of 6 sessions (2× week for 3 weeks)	8 responded while 6 had no effect. Efficacy rate of 57%. Increased serum albumin
Muso et al. [43] 1994, retrospective	8	16–56	Steroid resistant FSGS (6), MCNS (1) MN + FSGS (1)	Dextran sulfate cellulose adsorption	2–13 sessions (average of 7.3 sessions)	CR: 4 patients, PR: 1 patient and no effect in 3 patients. Efficacy rate of 63%
Tojo et al. [42], 1988, prospective	5	15–58	Drug resistant FSGS	Polyanionic dextran sulfate	Alternating 6–8 sessions of LDL-A and double filtration PP	Reduction in proteinuria with partial remission in 4 patients
Oto et al. [45], 2009, case report	1	8	FSGS (resistant to steroids, CPM, and CSA)	Dextran sulfate cellulose adsorption	5 session over 3 weeks plus CSA (65 mg/days), prednisolone (5 mg/kg/days) and methylprednisolone (800 mg/days) pulse therapy for 5 weeks before and 1 week after LDL-A treatment	Reduction in proteinuria to 0.5–1 g/day and hyperlipidemia
Shah et al. [1], 2019, prospective	7	19 months to 7 years	FSGS (recurrent)	Dextran sulfate cellulose adsorption	2–3 sessions per week for 3 weeks followed by weekly sessions for at least 6 weeks. Some patients received therapy for longer durations	All patients attained at least a 10-fold reduction in proteinuria (less than nephrotic range – 2.0 g.g). CR was achieved in 4 patients
Raina et al. [35], 2019, prospective	17	6–20	FSGS (recurrent or resistant to steroids)	Dextran sulfate cellulose adsorption	6 sessions (2× week for 3 weeks) followed by 1× week for 6 weeks. Total of 12 sessions	10 patients lost due to protocol deviation or to follow-up. 1/7 patients attained PR, 2/4 patients had CR/PR and 2/3 patients had CR/PR at 1, 3, and 6 month follow-up. All patients had improved or stable GFR

LDL-A, low-density lipoprotein apheresis; FSGS, focal segmental glomerulosclerosis; CPM, cyclophosphamide; CR, complete remission; CSA, cyclosporine A; GFR, glomerular filtration rate; MCNS, minimal change nephrotic syndrome; MN, membranous nephropathy; PP, plasmapheresis; PR, partial remission.

ment in proteinuria and cardiovascular comorbidities [46]. Lp-PLA2 is a biomarker that is involved in the oxidation of LDL into lysophosphatidylcholines (LPC) and oxidized fatty acids (FA) [47]. Uncontrolled PLA2 activity can lead to a rapid increase in intracellular levels of LPC and FA, which are both proinflammatory and known to cause atherogenesis [47]. The investigators of the trial proposed that LDL-A will efficiently be able to remove circulating Lp-PLA2 and other lipid metabolites, such as oxidized LDL, LPC, FA, and proinflammatory mediators, involved in pFSGS and rFSGS. They suggest that removal of these substances may lead to an improvement in proteinuria, limit the direct toxicity caused to podocytes, and improve cardiovascular and clinical morbidities [46].

Potentiation of Immunosuppression for the Treatment of in LDL Apheresis

Throughout various trials, the beneficial effects of LDL-A on the efficacy and response rate of glucocorticoids (GC) and CsA in drug-resistant individuals have been observed. Various studies have further investigated this effect and suggested that LDL-A improves the bioavailability of GC and CsA via normalization of elevated serum lipid levels [48–50]. In a study by Petrichenko et al. [48], the authors demonstrated the effect of VLDL on the number of GC receptors present in rat and human smooth muscle cells (SMC). SMC cells contain high-affinity, low-capacity binding sites for the synthetic analog of GC, [3H] dexamethasone. In this study, the addition of VLDL to cultured SMC led to a significant reduction in GC-specif-

ic binding sites with a two-fold increase in binding affinity for dexamethasone. Similarly, human fibroblasts with VLDL (60 μg protein/mL) showed a maximal inhibitory effect on binding [48]. Additionally, the authors showed that the reduction in the number of binding sites led to a partial loss of sensitivity to the hormone via the inhibitory effect of dexamethasone on the release of arachidonic acid and synthesis of prostaglandin I2 [48]. With these results, the authors proposed that VLDL can prevent the inhibitory effect of GC on arachidonic acid release and leads to a reduction of prostaglandin I2 formation by decreasing GC-specific binding sites. The authors also suggest that the reduction of GC-binding sites by VLDL may also be linked to an increase in polyunsaturated FA levels [48].

In a different study, Leon et al. [49] illustrated the effect on CsA uptake and CsA mediated toxicity in human embryonic kidney cells due to varying levels of LDL receptors (LDLr). In this study, LDLr expression was decreased using small-interfering RNA constructs, which reduced LDLr protein expression by 60%, while LDLr expression was increased using LDLr overexpression plasmids [49]. Through the study, the authors demonstrated a decrease in CsA cytotoxicity in cells with lower LDLr compared to control cells. Most importantly, LDLr overexpression cells showed an enhanced uptake of radiolabeled CsA [49]. In another study by Ingulli et al. [50], the authors reviewed the use of CsA in children with refractory NS to identify potential markers that may affect CsA efficacy. After regression analysis of various parameters (proteinuria, serum creatinine, serum cholesterol levels), the authors found that serum cholesterol levels were the only significant predictor of unresponsiveness. From these outcomes, the investigators suggested that severe hypercholesterolemia was responsible for the decrease in the uptake of CsA by the cell [50]. A possible reason includes the increase in binding of CsA to lipoprotein in patients with elevated serum cholesterol levels. Additionally, hypercholesterolemia was suggested to inhibit CsA uptake via downregulation of the LDLr complex in cells, leading to inhibition of LDL binding [50].

A Prospective Observation Survey on the Long-Term Effects of LDL-A in Japan

A number of clinical studies have investigated the beneficial effects of LDL-A; however, the level of clinical evidence is still inadequate. Therefore, a multicentric, prospective observational survey on the long-term effects of LDL apheresis on drug-resistant NS (POLARIS) was initiated in Japan [51]. This study evaluated the long-term (2 years after LDL-A treatment) remission rate and affecting associated factors in 44 adult patients with drug-resistant NS. The majority of patients in the study were found to have FSGS (28/44), followed by membranous nephropathy and MCNS [51]. The patients were treated with an average of 9.6 ± 2.7 LDL-A sessions. In this study, 47.7% (21/44) of patients attained remission of NS after 2 years. Eleven (25%) patients achieved complete remission, while 10 (22.7%) patients had partial remission (urinary protein <1.0 g/day). Additionally, the study identified the various clinical parameters, which showed a significant contribution to the beneficial outcomes [51]. These include serum total protein (4.9 ± 0.7 g/dL), eGFR (61 ± 27.2 mL/min/m^2), urinary protein (1.7 ± 1.8 g/day), triglycerides (240.2 ± 156.3 mg/dL), serum albumin (2.9 ± 0.8 g/dL), serum creatinine (1.2 ± 0.7 mg/dL), total cholesterol (194.3 ± 65.6 mg/dL), and LDL (83.1 ± 60.4 mg/dL) [51]. Although this study was limited by a small sample size and lack of control group, this study showed remission of drug-resistant NS in nearly half of the patients, regardless of the classification of the primary disease.

Dextran-Suflate Plasma Adsorption Lipoprotein Apheresis in Drug-Resistant FSGS: The First US Multicenter Trial

In a recent prospective, multicenter, single-arm intervention study, Raina et al. [52] reported the first study on the treatment of drug-resistant pFSGS with the Liposorber® LA-15 system. In this study, 17 patients underwent a total of 12 LDL-A sessions. For the first 3 weeks, the sessions were 2 times a week followed by once weekly for 6 weeks. Of the 17 patients, 6 were excluded due to 1 patient not starting treatment and the others with protocol deviations. Within the remaining 11 patients, only 10 patients had fully completed all 12 sessions. Three of the 10 patients were lost to follow-up immediately after LDL-A leaving 7 patients for outcome analysis [52]. In this study, follow-ups were performed at 1, 3, 6, 12, and 24 months following the last apheresis treatment. The authors reported a complete remission rate of 14.3% (1/7) at 1-month follow-up. Additionally, remission rates (partial/complete) of 50% (2/4) and 66.7% (2/3) were reported after the 3 and 6 months follow-ups, respectively [52]. At 12 months follow-up, 1 of the 2 patients attained complete remission, while the 1 patient who completed the 24 months follow-up had partial remission. Although many patients were lost to the follow-ups, all patients exhibited stable or improved eGFR. This study also includes several contradictions to the use of the Liposorber® LA-15 system [52]. These contradictions include the use of angiotensin-converting enzyme

inhibitors within 24 h of treatment, due to reported severe anaphylactoid reaction and shock. Other contraindications included individuals who could not tolerate anticoagulation and extracorporeal circulation and those that are allergic to any of the following components: heparin, dextran sulfate cellulose, and ethylene oxide [52]. Overall, this study is limited by a small sample size and high dropout rate; however, it showed improvement in the response rates to steroid/immunosuppressive therapy, induced remission of proteinuria, and improved or stabilized eGFR in all patients.

LDL-A-Induced Remission of FSGS Recurrence in Pediatric Renal Transplant Recipients

Recently, a case series by Shah et al. [1] evaluated the treatment effect of LDL-A in patients with early rFSGS. This study represents the first successful treatment of FSGS recurrence after pediatric renal transplantation via LDL-A since the FDA approval of the Liposorber® LA-15 system. Patients included in the study were from 4 different centers in the US and the United Kingdom. All patients were provided with 2–3 LDL-A sessions per week for the first 3 weeks with 10–20 mg/kg of pulsed IV methylprednisolone followed by weekly LDL-A sessions until discontinuation [1]. Immunomodulating therapies such as steroids, azathioprine, rituximab, cyclophosphamide, cyclosporine, abatacept, and plasmapheresis were also provided for the management of rFSGS. The authors reported corticosteroids, rituximab, and plasmapheresis as the most commonly used interventions. The plasmapheresis regimen varied between 2 and 3 sessions per week from 1 week to 18 months [1].

After plasmapheresis treatment, all patients underwent LDL-A for at least 9 weeks. As a result of varying LDL-A treatment, all patients demonstrated improvement in urinary protein to creatine ratios with 57% (4/7) of the patients achieving complete remission [1]. Though, the proteinuria levels of all patients were reduced to less than the nephrotic range of 2.0 g/g. Additionally, 86% (6/7) of patients showed significant improvement in estimated GFR from time of LDL-A initiation to the time of discontinuation. In conclusion, this case series demonstrated the successful treatment of 7 pediatric rFSGS patients with the Liposorber® LA-15 system [1]. Although the small sample size is a limitation of this study, the findings of this study support the need for larger, randomized, controlled studies to further provide verify the benefits of LDL-A in FSGS.

Overall, these studies were able to demonstrate the beneficial effects of LDL-A in drug resistant and rFSGS. Even though some of the studies were not limited to just the pediatric population, the majority of the patients exhibited a reduction in proteinuria and improvement in lipid abnormalities after LDL-A treatment. It is also important to note that LDL-A treatment was able to improve corticosteroid and cyclosporine action and responsiveness in patients with drug resistance. This may potentially be due to the restoration of cellular uptake and the inhibition of drug efflux. Lastly, additional randomized controlled studies with long-term follow-up are necessary to further justify the beneficial health outcomes of LDL apheresis in children.

Conclusion

FSGS remains a clinical challenge for many pediatric nephrologists. Advances in immunomodulating therapy have led to some improvement; however, drug resistance and intolerance have led to a minimal response in treatment. Various extracorporeal techniques are available at this time and have shown promise in the treatment of FSGS. Currently, the Liposorber® LA-15 system has shown to induce the remission of proteinuria in pediatric patients with both drug-resistant and recurrent FSGS. The initial data from the multicenter clinical trial evaluating the use of Liposorber® LA-15 are supporting the efficacy and safety of the system in its use in the treatment of FSGS. However, additional studies on LDL-A and further study of the system are needed in the pediatric population to further define the therapeutic outcomes.

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Author Contributions

All authors contributed equally to this manuscript.

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