Saturday, 9:30 – 10:15 a.m.

LDL-Apheresis as a New Treatment for FSGS

David M. Ward, MD, FRCP, HP(ASCP).
Professor of Medicine, Division of Nephrology, University of California San Diego.
Medical Director, Therapeutic Apheresis Program.
Associate Medical Director, Kidney/Pancreas Transplantation.
DISCLOSURES:
The speaker currently has these potential conflicts:

- Therapeutic Apheresis Program, UC San Diego
  - Medical Director, salaried
- TerumoBCT, Inc. – consulting, honoraria
- Support from multiple apheresis industry interests for conference “Essentials and Advances in Apheresis Therapies”, annually in San Diego. (5th annual will be February 23 - 25, 2017)

In the past 5 years:

- Therakos, Inc. – lecturing, honoraria
- Alexion Pharmaceuticals. – advisory board
- Aethlon Medical Inc. – consulting

WARNING:

- Non-approved uses: “Off-label” uses of drugs and devices will be discussed
APC  Apheresis Physicians’ College at UCSD

4-day immersion in the Apheresis Unit, with mentorship by experts. Round on 50+ procedures; one-on-one discussions; lectures and workshops. Limited to 3-5 participants. Offered 4 times per year. Contact dmward@ucsd.edu or nmgriffin@ucsd.edu
FSGS (Focal Segmental Glomerulosclerosis)

OUTLINE:

1. TPE for FSGS.
2. LDL-apheresis for FSGS.
3. What is going on in FSGS anyway?
4. Recommendations, insights and next steps
Clinical features:

- Mainly children, teenagers and young adults.
- Proteinuria, sometimes persistent hematuria.
- Nephrotic syndrome* in almost 100% of “Primary” type FSGS, ~ 50% of other subtypes of FSGS.
- Often hypertensive.
- Progressive renal failure: 70% reach end stage in 10 years.
- Recurs in kidney transplants (only “Primary” type FSGS)

*Nephrotic syndrome =

- heavy proteinuria (e.g. >3.5 g/day), enough to cause
- low serum albumin (e.g. <3 g/dL), low enough to cause
- edema, and also to cause secondary
- hypercholesterolemia.
Treatment:

- 20 - 40% of nephrotic cases may be helped by corticosteroids.
- Data also support use of cyclosporine, mycophenolate, cyclophosphamide, rituximab, etc.
- Use ACE-inhibitors or ARB’s (non-specific).

<table>
<thead>
<tr>
<th>Role of therapeutic apheresis</th>
<th>TPE</th>
<th>LDL-apheresis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>for post-transplant FSGS</td>
<td>Established (ASFA Category 1)</td>
<td>Meagre evidence</td>
</tr>
<tr>
<td>for native-kidney 1&lt;sup&gt;st&lt;/sup&gt; FSGS</td>
<td>Less evidence</td>
<td>Some evidence</td>
</tr>
</tbody>
</table>

* LDL-apheresis using dextran sulfate adsorption (Kaneka Liposorber®)
FSGS (Focal Segmental Glomerulosclerosis)

FSGS is a group of diseases of the renal glomeruli:

- Actually a pattern of response to injury that has multiple etiologies.
- The “Primary” type recurs in kidney transplants.

---

1972

**RECURRENT OF IDIOPATHIC NEPHROTIC SYNDROME AFTER RENAL TRANSPLANTATION**

John R. Hoyer                Leopoldo Raij
Robert L. Vernier              Richard L. Simmons
John S. Najarian               Alfred F. Michael

*Departments of Pediatrics, Internal Medicine, and Surgery, University of Minnesota Medical School, Minneapolis, Minnesota 55455, U.S.A.*

**Summary** Three patients with steroid-resistant idiopathic nephrotic syndrome were studied at onset and during recurrent nephrotic syndrome after renal transplantation. Renal biopsies at the onset of the nephrotic syndrome showed typical urine does not clear of protein and these patients progress to renal failure. We have studied four such patients at the onset of their disease and after renal transplantation. The nephrotic syndrome recurred in three of them shortly after renal transplantation.

**Case-reports**

**FIRST CASE**

This boy developed intermittent periorbital oedema at 7½ years of age. 6 months later the nephrotic syndrome was diagnosed (fig. 1). Prednisone 80 mg. per day for 21 days did not decrease proteinuria. 6 weeks later anasarca was present and laboratory studies demonstrated a nephrotic syndrome (table 1). 7 months later, laboratory studies were unchanged and prednisone 60 mg. per day was given for 20 days without decrease in proteinuria. 10 months later, when renal function was decreasing, azathioprine (‘Imu-
FSGS (Focal Segmental Glomerulosclerosis)

2012 Case report:
- 27 year old man, ESRD due to primary FSGS.
- Kidney transplant from sister.
- Day 2: recurrence of nephrotic syndrome (heavy proteinuria).
- Day 6: Biopsy - recurrence of FSGS (by biopsy of kidney transplant).
- Rapid loss of renal function, severe depletion of serum albumin.
- Day 14: Kidney removed and re-transplanted into a 66 year old man with ESRD (diabetic nephropathy).
- Immediate graft function with rapid reduction of proteinuria.
- Biopsies at day 8 & day 25 after re-transplantation - glomerular lesions returning to normal.

FSGS

TPE is established first-line effective treatment for recurrence of FSGS after renal transplantation.

Plasma exchange (TPE) for FSGS

for recurrent FSGS:

- Recurs post-transplant in ~ 23% of adults with primary FSGS.
- Recurrence rates higher in children.
- Recurrence rates higher if previous transplant loss to recurrence.
- TPE for post-transplant recurrence is well established (1-11).

for native-kidney FSGS:

- . . . less evidence.

(1) Zimmerman SW: *Nephron* 40:241-245, 1985

dmward@ucsd.edu
Primary FSGS:

- Plasma from patients with Primary FSGS can cause:
  - Proteinuria in experimental animals.
  - Shrinking of cultured glomeruli in vitro.
- Due to endogenous circulating glomerular permeability factor(s).
- Candidate molecules, none proven:
  - Small, highly glycosylated, hydrophobic protein(s) / peptide(s), 30 to 50 kDa, poorly characterized.
  - suPAR (soluble urokinase-type Plasminogen Activator Receptor).
  - CLC1 (Cardiotrophin-like cytokine 1).
  - others

Note all are < 50 kDa (molecular weight)
FSGS (Focal Segmental Glomerulosclerosis)

Proteinuria in newborn from mother with Primary FSGS:

![Graph showing proteinuria in newborn days after birth](image-url)
TPE (plasma exchange)

... works for Primary FSGS

Centrifugal TPE machines

Membrane TPE machines
Dextran Sulfate Adsorption Apheresis (Kaneka Liposorber®)

... works for hypercholesterolemia

- Removes LDL, Lp(a), and VLDL.
- Minimal effect on HDL or albumin.
- Effective LDL apheresis

Perfusion columns containing Dextran sulfate

FDA-approved for LDL
Dextran Sulfate Adsorption Apheresis (Kaneka Liposorber®)

... works for hypercholesterolemia

- 6 yr study of 130 heterozygous Familial Hypercholesterolemia with CHD
- Cardiovascular events: Group 1 = 10% , Group 2 = 36%

Fig. 3. Kalpan–Meier curves for endpoints in reduction of cardiovascular events (Mabuchi et al Am J Cardiol 82:1489-95, 1998)
Blood components removed:
- LDL cholesterol
- VLDL cholesterol
- Lp(a) cholesterol
- Plasma proteins (15%)
- Fibrinogen (29%)
- Vitamin E (55 - 63%)
- Platelets (17%)
- Others?

ApoB-lipoproteins (73% – 83%)

Not significantly removed:
- HDL cholesterol

[Slide courtesy of Amber P. Sanchez, MD]
Dextran Sulfate Adsorption Apheresis (Kaneka Liposorber®)

... works for (some cases of) FSGS

- 11 children with biopsy proven FSGS, all steroid-resistant after 8 weeks (and prior cyclosporin-A).
- Kaneka Liposorber® 2x per week for 3 weeks, then 1x per week for 6 weeks.
- 7 of 11 had marked reduction in proteinuria, or achieved remission.
- Appeared to improve response to steroids.


[Slide courtesy of Amber P. Sanchez, MD]
FDA approval for pediatric FSGS

- in October 2013
- Humanitarian Use Device application for Kaneka Liposorber.
- Pediatric FSGS indication:
  - children with
  - nephrotic syndrome,
  - proteinuria >3.5g/day,
  - hypoalbuminemia,
  - hyperlipidemia, and
  - progressive renal decline.
The POLARIS Trial
(Prospective Observational Survey on the Long-Term Effects of LDL Apheresis on Drug-Resistant Nephrotic Syndrome)

- 64 courses in 58 patients with steroid +/- cyclosporine resistant nephrotic syndrome, ages 18-84. (17 courses excluded for insufficient data).
- All treated on Kaneka Liposorber system (dextran sulfate adsorption).
- Average 9.6 LDL-A procedures per course.
- 3.5 L. (av.) plasma processed per procedure.
- 55% of courses were in patients with FSGS.
- Proteinuria fell similarly in FSGS cases (from 6.47 ± 2.98 to 3.26 g ± 3.13) non-FSGS cases (6.13±3.41 to 3.89+4.01).

Role of Lipids in Glomerulosclerosis

Hyperlipidemia contributing to glomerular damage:


Role of Lipids in Glomerulosclerosis

LDL-apheresis for non-FSGS causes of nephrotic syndrome

  - 7 adults with hypercholesterolemia due to nephrotic syndrome
  - Diseases other than FSGS (4 Memb GN, 2 MPGN, 1 IgAGN).
  - Treated with Dextran-sulfate apheresis (Kaneka columns).
  - All benefitted with regard to reduction of LDL and Lp(a).
  - Serum albumin increased (p=0.01),
  - Proteinuria tended to decrease (NS).
  - Confounding factors include immunosuppressive drugs.
LDL-apheresis for FSGS

Dextran-sulfate adsorption: possible mechanisms in FSGS

- Adsorption of glomerular permeability factors
- Correction of secondary hyperlipidemia
  - Nephrotic syndrome causes severe hyperlipidemia
  - Hyperlipidemia implicated in progression of glomerular and tubular injury
- Enhanced effectiveness of steroid therapy
  - Because VLDL induces a dose-dependent reduction in binding sites for dexamethasone (in vitro evidence).
- Other
  - Reduction in oxidized LDL & inflammatory cytokines
  - Decrease in vasoconstrictive eicosanoids (thromboxane A2 & prostaglandin I2)
  - Improved hypercoaguability (decreased Factor V, VIII, vWF, prekallikrein)
OUTLINE:

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Kidney \{ \sim 2 \text{ per person} \}

Nephron \{ 800,000 \text{ to } 1,000,000 \text{ per human kidney} \}

- Afferent arteriole
- Tubule
- Glomerulus
- Efferent arteriole
- Collecting duct
Normal Glomeruli

Focal = some glomeruli not affected
Segmental = some parts not affected

FSGS
Normal Glomerulus

- Bowman's capsule
- Bowman's space (urinary space)
- Mesangial cell body
- Mesangium
- Endothelial cell body
- Glomerular basement membrane (GBM)
- Capillary lumen
- Visceral epithelial (podocyte) cell body
- Parietal epithelium
Normal Glomerulus - Diagram

- Bowman’s capsule
- Bowman’s space (urinary space)
- Efferent arteriole
- Afferent arteriole
- Parietal epithelium
- Visceral epithelial (podocyte) cell body
- Glomerular basement membrane (GBM)
- Capillary lumen
- Endothelial cell body
- Mesangium
- Mesangial cell body

© David M Ward, 2014
Normal Glomerular Capillary Loop

- Capillary lumen
- Mesangial cell
- Mesangial matrix
- Glomerular basement membrane
- Podocyte foot processes
- Slit diaphragms
- Part of epithelial cell (Podocyte)

© David M Ward, 2012
Normal Glomerular Capillary Loop

Micrograph © The McGraw-Hill Companies Inc, 2011
Podocyte Foot Process Architecture
Normal Glomerular Capillary Loop

Podocyte Foot Process Architecture

Circulating glomerular permeability factors can cause **Minimal Change Nephropathy and Primary FSGS** by disrupting these mechanisms.

Genetic abnormalities of theses proteins can cause **familial FSGS-like diseases**.

**Podocyte Foot Process Effacement**

**Healthy:**
- Urinary filtrate
- Actin cytoskeleton
- Filtration slit
- Flow of molecules

**Collapsed / “effaced”:**
- Urinary filtrate
- Podocyte fusion and collapse
- Reorganization of actin cytoskeleton
- Albumin

Podocyte Foot Process Effacement

In Minimal Change Disease:
- podocyte effacement is reversible with steroids

In Primary FSGS:
- podocyte effacement
- progresses to podocyte cell death
- with consequent sclerosis of the underlying glomerular capillary tuft.

Electron micrographs courtesy Dr Lindskog Johnsson 2014
Normal Glomeruli

Focal = some glomeruli not affected
Segmental = some parts not affected

FSGS
**FSGS is a group of diseases**

<table>
<thead>
<tr>
<th>Etiology/mechanism</th>
<th>Example Focus</th>
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<tr>
<td>Primary FSGS</td>
<td>Circulating factors toxic to podocyte integrity.</td>
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<tr>
<td>Secondary FSGS</td>
<td>Adaptive injury (hyperfiltration damage).</td>
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<tr>
<td>Familial FSGS</td>
<td>Genetic defects of podocyte and slit-pore proteins.</td>
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<tr>
<td>“Collapsing” form of FSGS</td>
<td>Toxins &amp; viruses (HIV, parvo B19, pamidronate, etc.)</td>
</tr>
<tr>
<td>FSGS due to scarring from other GN</td>
<td>Non-specific scarring after inflammatory types of glomerulonephritis.</td>
</tr>
</tbody>
</table>

**FSGS is more common in African Americans.**

“Good gene, bad gene. The same gene variants that promote destruction of the kidney’s filtration units also combat *Trypanosoma brucei rhodesiense* parasites”.

- Two APOL1 variants are common in West African chromosomes.
- These variant genes produce a serum factor that lyses trypanosomes.
- But confers FSGS odds ratio of 10.5
- And hypertension-attributed ESRD odds ratio of 7.3

Leslie M. Science 329:263, 2010 (Editorial)
FSGS is a group of diseases

<table>
<thead>
<tr>
<th>Etiology/mechanism</th>
<th>Histological hallmarks</th>
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For trials of TPE and other therapies, important to ensure subjects have primary FSGS.
FSGS is a group of diseases

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**Predict**
- recurrence in transplant
- no response to TPE

**Predict**
- no recurrence in transplant
- no response to TPE
Study patients:
- 83 children with Primary FSGS.
- Mean age 13 years at first kidney transplantation.
- 53 cases analyzed for NPHS2 mutations (gene for Podocin).

Results:
- FSGS recurred in 30 patients (36%) (median 13 days; range 1.5 to 152 days).
- 23 patients received a second kidney transplant:
  - FSGS recurred in 11 (48%) (median 16 days; range 2.7 to 66 days).
- Recurrence of FSGS: 0% if NPHS2 mutations (homozygous or compound) versus 45% in patients without mutations.

Conclusion:
- Genetic testing worthwhile.
- Important for prognosis and treatment before and after transplantation.

Glomerular permeability factors – candidate molecules

- Small, highly glycosylated, hydrophobic protein(s) / peptide(s), 30 to 50 kDa, poorly characterized.
- suPAR (soluble urokinase-type Plasminogen Activator Receptor).
- CLC1 (Cardiotrophin-like cytokine 1).
- others
Glomerular Permeability Factors in FSGS

Candidate molecule:
Small, highly glycosylated, hydrophobic protein 30 to 50 kDa

- Poorly characterized because it disintegrates in vitro. (1)
- Permeability activity is decreased by plasmapheresis. (2)
- Proteinuric effect inhibited by galactose (3), but clinical benefit in FSGS patients given oral galactose (4, 5) now disproven.
- The GVV (Glomerular Volume Variability) assay – test plasma dripped on to cultured glomeruli as a biological assay of factor activity.

**Candidate molecule:**

**CLC1 (Cardiotrophin-like cytokine 1)**

- CLC1 is in IL-6 family (approx. 220 AA, 24kDa).
- Decreases nephrin expression in cultured podocytes.
- CLC1 inhibitors reverse the permeability effect of plasma from FSGS patients.
- Data are preliminary.

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Candidate molecule:
**suPAR** (soluble urokinase-type Plasminogen Activator Receptor)

2011: Research implicated “suPAR” present on podocytes:

- suPAR levels (22 to 45 kDa fragments) are elevated in 70% of patients with FSGS, but not in other glomerular diseases.

- In animal models, suPAR causes podocyte injury by activation of β3 integrin.

- In kidney biopsies, β3 integrin is found on podocytes in patients with FSGS (but not other diseases).

---

suPAR removal by plasmapheresis in recurrent FSGS (post-transplant)

- Initial studies of plasmapheresis (TPE):
  - clinical remission if suPAR levels <2,000 pg/ml.
  - serum no longer induces podocyte β3 integrin.

- In 2 patients:
  - TPE failed to reduce suPAR levels <2,000 pg/ml.
  - did not achieve clinical remission.
  - serum still strongly activated β3 integrin.

Further evidence for a pathogenic role of suPAR

**Study patients:** Two cohorts with biopsy-proven primary FSGS:
- 70 patients from the North America–based FSGS clinical trial (CT).
- 94 patients from European PodoNet study of steroid-resistant nephrotic syndrome.

**Results:**
- Elevated suPAR in 84.3% (CT) and 55.3% (PodoNet), versus 6% of controls (P=0.0001); inflammation did not account for this difference.
- Reduction of suPAR correlates with treatment and with reduction of proteinuria, with higher odds for complete remission (P=0.04).

**Conclusions:**
- suPAR levels elevated in geographically and ethnically diverse patients with FSGS.
- Reductions in suPAR levels correlate with different therapeutic regimens and with remission; this supports the role of suPAR in pathogenesis.

**Unexpected finding:**
- In the PodoNet cohort, patients with an NPHS2 mutation had higher suPAR levels than those without a mutation. (NPHS2 codes for Podocin.)

Contradictory evidence for a pathogenic role of suPAR


Cathelin D, et al. Administration of recombinant soluble urokinase receptor per se is not sufficient to induce podocyte alterations and proteinuria in mice. *JASN* 25:1662-1668, 2014

suPAR: 241 patients from the NEPTUNE observational study

“After adjusting for baseline suPAR concentration, age, gender, proteinuria, and time, the change in suPAR from baseline was associated with eGFR, but this association was not different for patients with FSGS as compared with other diagnoses. Thus these results do not support a pathological role for suPAR in FSGS.”

The Glomerular Volume Variation (GVV) test

The Glomerular Volume Variation (GVV) test - normal control

Unpublished - courtesy of Milos Budisavljevic, MD, (Professor, Division of Nephrology, Medical University of South Carolina)
The Glomerular Volume Variation (GVV) test - positive result

Unpublished - courtesy of Milos Budisavljevic, MD,
(Professor, Division of Nephrology, Medical University of South Carolina)
Control plasma: JW052410  
(Heart transplant rejection)

FSGS plasma: JD22511

Modified CVV test
- single glomerulus held on pipette tip
- controls and patient plasmas tested serially

(Wilcoxon Signed Rank Test: P=0.014  
n=11 glom)

(Paired t-test: P=0.897  
n=15 glom)
FSGS (Focal Segmental Glomerulosclerosis)

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TPE for post-transplant recurrence:

- TPE is 1st-line therapy (plus mycophenolate, cyclophosph or rituximab).
- ASFA (2013) recommendation:
  - TPE daily x 3 days, then 3+/per wk for the next 2 wks.
  - Then 2 - 3/wk until remission (monitoring urine protein quantitation and serum creatinine); can take weeks to months. (1, 2)
- Case Series:
  - 17 TPE treatments in each of 7 adults, all with functioning transplants 10 months later. (3)
  - Remission rates of 80% in adults (4)
  - Remission rate of 88% in children. (5)

---

TPE for peri-transplant prophylaxis:

- 10 patients at high risk because of rapid progression (4) or prior recurrence in a transplant (6) received 8 TPE treatments in the peri-operative period.
  - 3 had recurrence within 3 months (all had prior graft loss to recurrence); 2 developed ESRD, 3rd with significant renal dysfunction.
  - 7 (including 3 with prior graft loss to recurrence) were free of recurrence at follow-up (238–1258 days), mean creatinine 1.53 mg/dL. (1)

- More recently, in 34 pediatric transplant cases, prophylactic TPE post-transplant appeared not to confer any outcome benefit compared with treatment of actual recurrence. (2)

---

TPE for primary FSGS (in native kidneys):

- TPE (averaging 17 treatments) plus corticosteroids and cyclophosphamide achieved sustained remissions in 8 of 11 previously unresponsive adults. (1)
- TPE (six treatments) without consistent immunosuppressive drugs reduced proteinuria in only 2 of 8 patients. (2)
- Expert opinion “based on very limited experience” (3):
  “Consider TPE for
  - Severe disease manifestations despite an adequate trial of initial immuno-suppressive therapy, in which very high levels of circulating permeability factor have been demonstrated.
  - Continued massive proteinuria and hypoalbuminemia despite exposure to an adequate course of prednisone, cyclosporine, and mycophenolate.”

(3) Appel GB and Cattran DC. Treatment of primary FSGS. In “UpToDate” ® online.
What does TPE do for FSGS?

Conventional plasma exchange (with albumin replacement):

- Established first-line treatment for recurrent FSGS (1-9)
- Sometimes useful pre-transplant in primary FSGS
- Removes macromolecules of all sizes:
  - IgG (140 kDa)
  - suPAR (22 to 45 kDa)
  - Ill-defined permeability factors (30 to 50 kDa)
  - CLC1 (24 kDa), etc., etc.
  - LDL-cholesterol (and other lipids)

---

(1) Zimmerman SW: Nephron 40:241-245, 1985
What does LDL-apheresis do for FSGS?
What does LDL-apheresis do for FSGS?

- Removes Glomerular Permeability factors (as efficiently as TPE)?
- Eliminates nephrotic syndrome in a majority of cases of primary FSGS?

Hattori et al, 2003

- Reduces hypercholesterolemia that contributes to glomerular damage?
- Somewhat improves proteinuria in a variety of nephrotic diseases?

Muso et al, 2015
LDL Apheresis - systems available worldwide

**LDL removal from separated plasma**

1. Adsorption
   - Liposorber (Dextran sulfate adsorption) *
   - TheraSorb LDL (Anti-ApoB immunoadsorption)

2. Precipitation
   - H.E.L.P. (Heparin-induced precipitation) *

3. Filtration
   - Double Filtration Plasmapheresis (DFPP)

**Direct LDL adsorption from whole blood**

- Liposorber D (Dextran sulfate adsorption)
- Direct Adsorption of Lipoprotein (DALI) (Polyacrylate adsorption)

* = FDA-approved
H.E.L.P. system LDL-Apheresis

B. Braun “Plasmat Futura”®

Heparin-induced Extracorporeal LDL-Cholesterol Precipitation

Blood return

Purified plasma

Acid buffer/heparin

Whole plasma

Acidity (pH 5.12) plus heparin causes precipitation of lipoprotein complexes

Precipitate filter captures lipoprotein complexes

Ultrafilter to correct pH and volume

Heparin adsorber

FDA-approved for LDL

No evidence - no reported use in FSGS.
Double-filtration (cascade) plasmapheresis (DFPP):

- Returns albumin (67 kDa) and all smaller molecules to the patient.

#1: Plasma-filter
Pore size: large
Cut-off: >2000 kD

Membrane specifications are those of Asahi products
(Asahi Kasei Kuraray Medical Co., Tokyo 101-8, 101, Japan)

Diagram from
J Clin Apheresis
26:230-238, 2011

#2: Plasma-fractionator
Pore size: medium
Cut-off: ~ 100 kD

#2: Plasma-fractionator
Pore size: medium
Cut-off: ~ 100 kD

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Size (kDa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>~3000</td>
</tr>
<tr>
<td>IgM</td>
<td>~ 970</td>
</tr>
<tr>
<td>IgG</td>
<td>~ 140</td>
</tr>
<tr>
<td>Albumin</td>
<td>~ 67</td>
</tr>
<tr>
<td>Permeability factors</td>
<td>&lt; 50 kDa</td>
</tr>
</tbody>
</table>

A few DFPP cases reported together with LDL-apheresis cases in FSGS publications.
Immunoadsorption (IA):

**Anti-IgG columns**

- Some reports say effective for recurrent FSGS. (1, 2)
- But they remove IgG, not lipoproteins or small proteins <50 kDa.
  
  Example: Globaffin ® columns use peptide ligand PGAM146 to adsorb IgG (Fresenius, Germany).
- One case report using Globaffin IA vs TPE claims effectiveness of IA. (3)

---

Case report using Globaffin IA vs TPE

*“Podocyte AP5 activity” = bioassay for podocyte β3 integrin activation by AP5 staining quantitated by mean fluorescence intensity (MFI)*

Weak evidence for use in FSGS

Impression:
- Claims for effectiveness of immunoadsorption (IA) or double-filtration (DFPP) are based on minimal evidence:
  - IA removes IgG but not LDL or proteins <50 kDa.
  - DFPP removes IgG and LDL but not proteins <50 kDa.

Other column adsorption apheresis:
Protein A columns
- Only one report of effectiveness for recurrent FSGS (1)
- Removes IgG, but not LDL or small proteins <50 kDa, etc.

Tryptophan adsorption column:
- One center reports “Effective for steroid resistant FSGS”. (2)

Conclusions:

- TPE is of major clinical benefit in FSGS (post-transplant recurrent type), by removal of Circulating Permeability Factor(s).
- LDL-apheresis in non-FSGS nephrotic syndrome reduces proteinuria to a lesser degree, perhaps by a different mechanism (reduction of nephrotoxic lipids).
- The efficacy of LDL-apheresis (dextran-sulfate adsorption) in FSGS could be due to either or both of these mechanisms.
- Until there is clarification, conventional TPE remains the most secure choice for FSGS (1).
- Elucidation of the mechanism and effectiveness of LDL-apheresis for FSGS should be achievable using existing techniques.

Suggested approaches to the validation of LDL-apheresis (Dextran Sulfate Adsorption) for FSGS:

- Trials in post-transplant recurrence to prove non-inferiority to standard TPE.
- Perform trials where native kidney disease is Primary FSGS (by clinical and biopsy EM criteria).
- Measure glomerular permeability factor by bio-assay of plasma (pre- and post-apheresis; pre- and post-column) (using Glomerular Volume Variation test or podocyte cultures).
- If bioassays are positive, dextran sulfate in vitro might help isolate the pathogenic factor(s) from TPE-derived plasma.
- Dr Budisavljevic and I would like to hear from anyone doing LDL-apheresis for FSGS.
SUMMARY:

1. TPE for FSGS.
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Thank you for your attention