Management of Nephrotic Syndrome

Treatment Strategies and Current Therapeutic Options

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DISCLOSURE STATEMENTS

Dr. Rovin has the following relevant financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

<table>
<thead>
<tr>
<th>Affiliation / Financial Interest</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Grants</td>
<td>NIH, Mallinckrodt</td>
</tr>
<tr>
<td>DSMB/Adjudication</td>
<td>Takeda</td>
</tr>
<tr>
<td>Medical/Scientific Advisor</td>
<td>Biogen, Mallinckrodt, Lilly, GSK, A-Z, Genentech, Pfizer, BMS, BioMarin, Aurinia</td>
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</tbody>
</table>

Unapproved or Off Label Disclosures

This presentation may discuss unapproved or off-label, experimental or investigational use of Cyclophosphamide, MMF, AZA, Rituximab, CSA
Non-Specific Anti-Proteinuric Therapies

- RAAS Blockade
- Reduce sodium intake to 2-3 g/d
- Reduce systolic blood pressure to 120 mm Hg
- Reduce protein intake to 0.7-0.8 g/kg/d
High Sodium Diet Negates Anti-Proteinuric Effects of ACEi

Heeg et al., KI, 1989
KDIGO GN Practice Guidelines

Specific Treatment of:

- Minimal Change Disease
- Focal Segmental Glomerulosclerosis
- Primary Membranous Nephropathy
Adult Minimal Change Disease

**Initial Episode**
- Prednisone (1mg/kg/d; Max 80 mg/d)
- Continue until CR (≥4wks; ≤16 wks)
- Taper over 6 months
- ALTERNATIVE: CYC 2-2.5 mg/kg/d for 8wks

**No Response to Steroids**
- 25% of patients
  - CYC 2-2.5 mg/kg/d
    - 8wks
  - Relapse >50% of patients
    - Frequent Relapses
      - Steroid Dependent
      - As for Initial Episode
    - Occasional Relapse
      - As for Initial Episode
    - Intolerant to Steroids, CYC, CNI

**As For Initial Episode**
- CNI
  - CSA 3-5 mg/kg/d; TAC 0.05-0.1mg/kg/d
  - After 3 months of remission taper to lowest dose that maintains remission for 1-2 years then taper off

**Relapse**
- >50% of patients
  - 30% of patients
    - As for Initial Episode
  - Frequent Relapses
    - Steroid Dependent
  - Occasional Relapse
    - As for Initial Episode

**MMF**
- 1-2g/d
  - 1-2 years
Reserve Immunosuppression for patients who have:
- Proteinuria >4g/d for at least 6 months
- Appropriate blood pressure control and treatment with RAAS inhibition
- SCr <3.5mg/dl and non-atrophic kidneys

Cyclical cyclophosphamide and prednisone for 6 months

CNI
CSA 3.5-5 mg/kg/d
TAC 0.05-0.075mg/kg/d
Prednisone 0.15mg/kg/d

Resistance

Resistance
Adult Focal Segmental Glomerulosclerosis

Primary FSGS Nephrotic Syndrome

- Prednisone (1mg/kg/d; Max 80 mg/d)
- Continue until CR (≥4wks; ≤16 wks)

Primary FSGS Non-Nephrotic

- RAAS Blockers; BP Control

CR

Taper prednisone over several months

Resistance

CNI
- CSA 3-5 mg/kg/d; level 125-175 ng/ml
- TAC 0.1-0.2mg/kg/d; level 5-10 ng/ml
- Prednisone 0.15mg/kg/d

Remission

Taper slowly after 1 year

No remission by 6 months

STOP

MMF, AZA??
FSGS-Primary or Secondary?

- FSGS is a lesion not a disease
- FSGS can be the result of a variety of pathogenic processes
  - Primary FSGS
  - Genetic Mutations in Podocyte Genes
  - Secondary FSGS
    - Viral: HIV, Parvo B19, SMV40 CMV
    - Drugs: Heroin, Interferon, Palmidronate, Sirolimus, CNIs
    - Adaptive: ↓nephron mass, obesity, GBM defects, healing focal proliferative GN, HTN, Sickle Cell Anemia, TMA
- Light Microscopy alone cannot discriminate between causes of FSGS

Courtesy of Dr. Fernando Fervena, Mayo Clinic
Primary vs Secondary FSGS

CLINICAL
• Nephrotic range proteinuria: >3.5g/24 hours
• Nephrotic syndrome: Nephrotic range proteinuria + hypoalbuminemia + edema + lipiduria + hyperlipidemia
• Many conditions give rise to nephrotic proteinuria but not nephrotic syndrome
• This is an important clinical distinction because nephrotic range proteinuria without edema or hypoalbuminemia is more likely to be due to secondary FSGS as opposed to primary FSGS

HISTOLOGIC
• Primary FSGS is generally associated with diffuse foot process effacement

Courtesy of Dr. Fernando Fervena, Mayo Clinic
Primary vs Secondary FSGS

FSGS lesion on renal biopsy (except collapsing)

- Nephrotic syndrome (proteinuria >3.5 g/24 hr + serum albumin <3.5 g/dL)
  - Yes
  - Primary FSGS
  - No

- Electron microscopy (foot process effacement)
  - Widespread >80%
  - Secondary FSGS
  - Segmental <80%

Courtesy of Dr. Fernando Fervena, Mayo Clinic
Quality of Evidence

MCD
- Corticosteroids for Initial Episode (1C)
- Cyclophosphamide for Frequent Relapses/Steroid Resistance (2C)
- CNIs for Relapses after Cyclophosphamide (2C)

FSGS
- Corticosteroids for Initial Episode (2C)
- CNIs for Initial Episode (2D)
- CNIs for Steroid Resistance (2B)

MN
- Cyclical Cyclophosphamide/Corticosteroids for Initial Episode (1B)
- CNIs for Initial Episode (1C)

Level | Grade: overall quality of evidence
1=recommended | A=high
2=suggested | B=moderate
              | C=low
              | D=very low
Unmet Needs in Treatment of Primary Nephrotic Syndromes

- Resistance to current treatments
- Dependence on steroids
- Toxicity of current treatments
Novel Approaches to Therapy*

- Abatacept
- Adrenocorticotropic Hormone Gel
- Rituximab

*Note: There have been no major randomized clinical trials testing these novel approaches completed to date
Mechanisms of Action

- Immunomodulation
- Podocyte Protection
Immunomodulation

**T Cells**
- CD28
- B7-1 (CD80)
- Abatacept

**APCs**
- B7-1

**Co-Stimulatory Blockade**

**Leukocytes**
- ACTH
- MCR
- ↑CREB
- ↓NFκB
- ↑PKA
- ↑anti-inflammatory cytokines
- ↓pro-inflammatory cytokines

**B Cells**
- CD20
- RITUX
- X
- IgS
- Cytokines
- T Cell Help
- Help
Podocyte Protection: Abatacept

Normal Podocyte; β1 Integrin Active; Podocyte Stays Put

Subset of Proteinuric Patients

B7-1 (CD80) Expressing Podocyte

Abnormal Podocyte; β1 Inactive; Podocyte Can Migrate → Proteinuria

Abatacept Protects Podocyte by Restoring β1 Activation
Podocyte Protection: ACTH

Normal Podocyte

Effaced Podocyte

Proteinuric Kidney Disease

ACTH

↑Rho

↑CdC42

↑PKA

↑RAC

Normal Podocyte

Restoration of Podocyte Cytoskeletal Integrity

GBM

GBM

GBM

GBM
Podocyte Protection: Rituximab

Normal Podocyte

Proteinuric Kidney Disease

Effaced Podocyte

Ceramide

SMPDL-3B

ASMase

RITUX

FSGS Proteinuria Factor

SMPDL-3B

ASMase

FSGS Proteinuria Factor

• SMPDL-3b: Acid sphingomyelinase-like phosphodiesterase 3b contains an amino acid sequence that rituximab can bind to; actual function not clear
• ASmase: Acid sphingomyelinase, catalyzes conversion of membrane sphingomyelin to ceramide, as second messenger;

Restoration of Podocyte Cytoskeletal Integrity

GBM

GBM

GBM

GBM
Abatacept in MCD and FSGS

- In a subset of patients with MCD, FSGS, MN and lupus, podocytes were found to stain for B7-1 (CD80)

- Abatacept was tested in B7-1 positive FSGS

- 4 post-transplant patients with rituximab-resistant, recurrent FSGS, and one with steroid-resistant primary FSGS were treated

- All 4 transplant patients received one or two doses of abatacept, the primary FSGS patient received monthly dosing, and over 10-48 months of follow-up nephrotic proteinuria resolved and uPCR was maintained at 0.05-0.50.
Counter Point—Abatacept in MCD and FSGS

• Data are inconclusive

• The proposed mechanism of action, restoration of podocyte β1-integrin activity through an interaction of abatacept with podocyte B7-1 seems unlikely

• There is an ongoing clinical trial of abatacept in multi-drug resistant or multi-drug intolerant FSGS and MCD (NCT0259278)

Garin et al., Ped Nephrol, 2015; Delville et al, JASN, 2016
ACTH was given at a dose of 40-80 mg/d for 12 days

On 14 of the 15 occasions the albuminuria increased during treatment but diminished in all cases within six days after hormone treatment…It would appear that albuminuria is increased during the first few days of the administration of A.C.T.H. to patients with nephrosis, then lessens before or immediately after treatment is stopped, whether or not a diuresis takes place. On 12 occasions the albuminuria decreased but returned to its former gross levels; in two instances it disappeared and has not recurred after six months.
# ACTH Gel and Membranous Nephropathy

<table>
<thead>
<tr>
<th>ACTH Dose (units)</th>
<th>Duration of ACTH (MO)</th>
<th>F/U MO</th>
<th>eGFR</th>
<th>Baseline Proteinuria</th>
<th>Prior IS</th>
<th>Final Proteinuria</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 2X/wk</td>
<td>6</td>
<td>8</td>
<td>&gt;60</td>
<td>4851</td>
<td>MMF, CNI</td>
<td>400</td>
<td>CR</td>
</tr>
<tr>
<td>80 2X/wk</td>
<td>6</td>
<td>6</td>
<td>21</td>
<td>6749</td>
<td>MMF, CNI</td>
<td>1540</td>
<td>PR</td>
</tr>
<tr>
<td>80 2X/wk</td>
<td>6</td>
<td>6</td>
<td>58</td>
<td>4598</td>
<td>Steroid + CTX, CNI, MMF</td>
<td>1240</td>
<td>PR</td>
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<tr>
<td>80 2X/wk</td>
<td>6</td>
<td>6</td>
<td>57</td>
<td>8153</td>
<td>Steroid + CTX, CNI, MMF</td>
<td>1935</td>
<td>PR</td>
</tr>
<tr>
<td>80 2X/wk</td>
<td>6</td>
<td>6</td>
<td>30</td>
<td>8000</td>
<td>Steroid, MMF, CNI</td>
<td>3000</td>
<td>PR</td>
</tr>
<tr>
<td>80 2X/wk</td>
<td>5</td>
<td>12</td>
<td>&gt;60</td>
<td>8900</td>
<td>None</td>
<td>6000</td>
<td>NR</td>
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<tr>
<td>40 2X/wk</td>
<td>12</td>
<td>14</td>
<td>&gt;60</td>
<td>3469</td>
<td>Steroid + CTX</td>
<td>340</td>
<td>CR</td>
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<tr>
<td>80 q72 hours</td>
<td>11</td>
<td>11</td>
<td>25</td>
<td>9150</td>
<td>Steroid + CNI</td>
<td>2948</td>
<td>PR</td>
</tr>
<tr>
<td>40 3X/wk</td>
<td>6</td>
<td>7</td>
<td>20</td>
<td>11911</td>
<td>Steroid + CTX</td>
<td>13,330</td>
<td>NR</td>
</tr>
<tr>
<td>40 3X/wk</td>
<td>6</td>
<td>6</td>
<td>&gt;60</td>
<td>5700</td>
<td>Steroid + CTX</td>
<td>694</td>
<td>PR</td>
</tr>
<tr>
<td>80 2X/wk</td>
<td>12</td>
<td>13</td>
<td>40</td>
<td>2625</td>
<td>Steroids, CNI, CTX</td>
<td>240</td>
<td>CR</td>
</tr>
</tbody>
</table>

Bomback et al, Drug Des Devel Therap, 2011
ACTH Gel and PLA2R in Membranous Nephropathy

Hladunewich et al, NDT, 2014
ACTH Gel and FSGS

- 24 patient from two institutions
- All with idiopathic FSGS
- Mostly refractory or difficult to control
- Study is a combination of prospective and retrospective data
- Study is not blinded or controlled
- Follow up and duration of ACTH was not uniform
- ACTH regimens were not uniform

- Stanford Protocol: ACTH gel 40u SC weekly for 2 weeks, 80u SC weekly for two weeks, 80u SC twice a week to complete 16 weeks
- Columbia Protocol: 80 u SC twice weekly for 24 weeks
- Individual: Average 80 u SC twice weekly

### Table

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>45.3±15.8</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>White</td>
<td>20</td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
</tr>
<tr>
<td>FSGS Morphology</td>
<td></td>
</tr>
<tr>
<td>Tip</td>
<td>11</td>
</tr>
<tr>
<td>NOS</td>
<td>8</td>
</tr>
<tr>
<td>Cellular</td>
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<td>Collapsing</td>
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<tr>
<td>Previous IS Drugs</td>
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</tr>
<tr>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Steroid Dependent</td>
<td></td>
</tr>
<tr>
<td>Steroid Resistant</td>
<td>6</td>
</tr>
<tr>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Steroid Dependent</td>
<td></td>
</tr>
<tr>
<td>Steroid Resistant</td>
<td>3</td>
</tr>
</tbody>
</table>

Hogan et al., CJASN, 2013
Results

- 7/24 patients has some type of remission; 71% failed to achieve remission
- Median time to decreased proteinuria after ACTH was 5 weeks (range, 2-16 weeks)
- Median time to a remission after ACTH was 16 weeks (range, 5-18 weeks)
- 5/7 has sustained remission over median 90 week follow-up (range, 23-104 weeks)
- No clinical feature differentiated responders from non-responders
- 23/52 reported adverse events were corticosteroid-like, 1 pneumonia, 4 URI, no HTN or increase in BMI

**CONCLUSION: Discontinue ACTH if no proteinuria response by 12-16 weeks**

Responders

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IS During Treatment</th>
<th>Duration of ACTH (WK)</th>
<th>Initial SCr (mg/dl)</th>
<th>Final SCr (mg/dl)</th>
<th>Initial Proteinuria (g/d)</th>
<th>Final Proteinuria (g/d)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual</td>
<td>TAC</td>
<td>36</td>
<td>1.1</td>
<td>0.7</td>
<td>5.2</td>
<td>1.5</td>
<td>Partial</td>
</tr>
<tr>
<td>Columbia</td>
<td>None</td>
<td>24</td>
<td>1.2</td>
<td>1.4</td>
<td>2.1</td>
<td>0.27</td>
<td>Complete</td>
</tr>
<tr>
<td>Individual</td>
<td>None</td>
<td>36</td>
<td>3.6</td>
<td>1.3</td>
<td>15.2</td>
<td>0.9</td>
<td>Partial</td>
</tr>
<tr>
<td>Stanford</td>
<td>None</td>
<td>16</td>
<td>1.0</td>
<td>1.1</td>
<td>7.2</td>
<td>1.9</td>
<td>Partial</td>
</tr>
<tr>
<td>Stanford</td>
<td>None</td>
<td>16</td>
<td>0.6</td>
<td>0.7</td>
<td>4.3</td>
<td>0.27</td>
<td>Complete</td>
</tr>
<tr>
<td>Stanford</td>
<td>None</td>
<td>16</td>
<td>1.1</td>
<td>1.2</td>
<td>6.6</td>
<td>2.1</td>
<td>Partial</td>
</tr>
<tr>
<td>Columbia</td>
<td>None</td>
<td>24</td>
<td>2.3</td>
<td>1.3</td>
<td>5.0</td>
<td>0.96</td>
<td>Partial</td>
</tr>
</tbody>
</table>

Hogan et al., CJASN, 2013
ACTH-Summary

- In the modern era, the most compelling data for ACTH are in membranous nephropathy

- Although data are not from a RCT, ACTH may have some benefit in IS-refractory MN

- In MN ACTH may act through immunomodulation, as seen by its effect on PLA2R

- Data for resistant FSGS are less convincing and the number of reported patients is small

- There is an ongoing clinical trial of ACTH gel in treatment resistant or treatment intolerant FSGS (NCT02633046)
Rituximab and Primary MN

In the only RCT the primary endpoint of complete and partial response at the end of the trial (6 months) was not different between RAAS and RAAS+Rituximab; The Rituximab group did better only after longer follow-up in the non-RCT observational period

- 12 Studies
- n=428
- SCr: 115 (88-186)
- Prot: 9.1 (2.3-13)
- % Response: 67 (0-100)

ISSUES
- Few RCTs
- No comparison to current SOC treatments
- Lack of long-term follow-up to understand relapse rates and kidney survival

Relationship of anti-PLA2R and Proteinuria in Rituximab-Treated Patients

In many patients there is a lag between the fall in antibody and resolution of proteinuria, consistent with attenuating the auto-immune process and repair of kidney injury. Similar findings are seen with cyclophosphamide. Expecting a resolution of proteinuria within 6 months of rituximab treatment may be overly optimistic!
## Rituximab and Steroid-Dependent or Frequently Relapsing Adult Minimal Change Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>N</th>
<th>Rituximab Dosing</th>
<th>Outcome Measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Retrosp Case Series</td>
<td>17</td>
<td>Variable</td>
<td>Relapses after rituximab</td>
<td>65% had no relapses at mean f/u 26.7 months; 70% had withdrawal of steroids and other drugs after 1 year</td>
</tr>
<tr>
<td>2</td>
<td>Retrosp Chart Review</td>
<td>41</td>
<td>Variable</td>
<td>CR: PCR&lt;0.3 + withdrawal of all IS; PR: PCR&lt;0.3 + withdrawal of at least 1 IS drug</td>
<td>61% complete clinical response; 17% partial clinical response</td>
</tr>
<tr>
<td>3</td>
<td>Prosp Historical Controls</td>
<td>25</td>
<td>375 mg/m² q/6 months X 1 year</td>
<td>Relapses after 1 year of ritux compared to the previous year</td>
<td>4/25 relapsed compared to 25/25 prior to rituximab</td>
</tr>
<tr>
<td>3</td>
<td>Prosp Historical Controls</td>
<td>25</td>
<td>375 mg/m² q/6 months X 2 years; then 5 patients stopped ritux and 20 continued</td>
<td>Number of relapses before and after therapy</td>
<td>108 relapses in 24 months before rituximab and 8 in the 24 months after CR maintained in all patients at 24 months, one relapse in the discontinuation group 8 months after therapy stopped</td>
</tr>
</tbody>
</table>
# Rituximab and FSGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>N</th>
<th>Rituximab Dosing</th>
<th>Outcome Measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Retrosp Case Series</td>
<td>8</td>
<td>375 mg/m² X 4 or more doses</td>
<td>Proteinuria and SCr</td>
<td>SCr worsened; 5 patients had no proteinuria improvement, 1 had transient improvement, 2 had decline but still &gt;3g/d</td>
</tr>
<tr>
<td>2</td>
<td>Retrosp Chart Review</td>
<td>4</td>
<td>375 mg/m² X1</td>
<td>Complete Remission</td>
<td>CR only in the two patients who were steroid-dependent; Steroid-resistant patients did not achieve CR</td>
</tr>
<tr>
<td>3</td>
<td>Prosp Patient serves as their own control</td>
<td>8</td>
<td>375 mg/m² X 1</td>
<td>Nephrotic relapses in the year after rituximab compared to the year before rituximab</td>
<td>5-fold decrease in relapse rate in the steroid-dependent FSGS patients</td>
</tr>
</tbody>
</table>

- In recurrent FSGS post-transplant 4 adults were reported; all patients received plasmapheresis + rituximab; 2 patients had a complete remission and 2 had partial remission

Rituximab-Summary

• The most compelling data for rituximab so far are in primary membranous nephropathy and minimal change disease.

• Rituximab is currently being used in one arm of a RCT (MENTOR).

• In MN rituximab may act through immunomodulation, as seen by its effect on PLA2R.

• Data for resistant FSGS are less convincing and the number of reported patients is small.