Primary Glomerulonephritides
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Rush University Medical Center
Chicago, Illinois

Idiopathic Nephrotic Syndrome in Adults

Korbet AJKD 1996, Haas AJKD 1997

MINIMAL CHANGE DISEASE

Secondary Causes of MCD

Idiopathic  48  87%
Secondary  7  13%
Lithium  0
NSAIDs  5
Lymphoma  2
Warren AJKD 1989
Presenting Characteristics in Adult MCD

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>89</td>
<td>40</td>
<td>33</td>
<td>51</td>
<td>398</td>
</tr>
<tr>
<td>Age</td>
<td>42±19</td>
<td>41±20</td>
<td>28±11</td>
<td>37±11</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Male</td>
<td>56%</td>
<td>33%</td>
<td>67%</td>
<td>70%</td>
<td>60%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30%</td>
<td>21%</td>
<td>9%</td>
<td>47%</td>
<td>21%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>28%</td>
<td>21%</td>
<td>15%</td>
<td>33%</td>
<td>23%</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>61%</td>
<td>18%</td>
<td>15%</td>
<td>56%</td>
<td>32%</td>
</tr>
<tr>
<td>SAib (g/dl)</td>
<td>1.9±0.7</td>
<td>1.8</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPro (g/24h)</td>
<td>10±6</td>
<td>12.4</td>
<td>16.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Controlled Trial of Prednisone in Adult MCD

Proportion with proteinuria >1 g/24h

Complications of Nephrotic Syndrome in Adult MCD

| Complication      | n 19/89 (21%) | Thrombosis 12 (13%) | Major Infection 10 (11%) | ARF 10 (11%) | MI 2 (2%) |

Adult MCD with ARF

<table>
<thead>
<tr>
<th></th>
<th>No ARF SCr&lt;1.5 mg/dl</th>
<th>ARF SCr&gt;2.0 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
<td>21 (30%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Age</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>138</td>
<td>158</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Proteinuria (g/24h)</td>
<td>8.0</td>
<td>14</td>
</tr>
<tr>
<td>Arteriosclerosis (0-4)</td>
<td>0.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>

All patients recovered
Initial Response to Steroids in Adult MCD

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>91%</td>
<td>94%</td>
<td>97%</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td>Complete</td>
<td>78%</td>
<td>91%</td>
<td>97%</td>
<td>76%</td>
<td>95%</td>
</tr>
<tr>
<td>Partial</td>
<td>13%</td>
<td>3%</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid Resistant</td>
<td>9%</td>
<td>6%</td>
<td>3%</td>
<td>8%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Response in MCD

- Nakayama et al, AJKD 2002

Nakayama et al, AJKD 2002

Adult MCD: Daily vs Alternate Day Steroids

- 95 Nephrotic adults with MCD
- 80% white, 7% black, 5% Hispanic
- Age: 45yo, Male: 61%
- SCR: 1.39 mg/dl, SAib: 2.2 g/dl, UPro: 10 g/d
- Treatment:
  - Daily steroids (1 mg/kg/d for 26 wks): 65 pts
  - Alternate day steroids (2 mg/kg/qod for 26 wks): 23 pts
- Remission:
  - CR = UPro <0.3 g/d
  - PR = 50% reduction in UPro from baseline
- Baseline features similar among the 2 groups

Waldman, Appel et al, CJASN 2007

Time to Remission

- Time to remission: 13 wks

Waldman, Appel et al, CJASN 2007
**Duration of Remission in Adult MCD**

- Nakayama et al, AJKD 2002

**Types of Relapse in MCD**

1. Occasional Relapser
2. Frequent Relapser: ≥2 within 6 mos or ≥4 in 12 mos
3. Steroid Dependent: 2 relapses on steroid taper or within 1 mo of ending treatment

**Adult MCD: Daily vs Alternate Day Steroids**

- Relapse: 73%
- More than 1 relapse: 44%
- Frequent relapers: 28%
- Remissions with 2nd line therapies similar but SD (82%) responded better SR (43%, p 0.01)
- ESRD: 4 pts
  - All SR and 3 had FSGS on 2nd biopsy
- Complications similar QOD vs Daily steroids

**Steroid-Dependent Adult MCD: Response to Second Line Agents is Similar**

- Waldman, Appel et al, CJASN 2007
### Treatment of SD/FR in Nephrotic Children

- Cyclophosphamide v Prednisone (RR- 0.44)
- Chlorambucil v Prednisone (RR- 0.15)
- No difference in relapse rate at 2 yr for CYC v Chlor
- CSA as effective as CYC and Chlor
- MMF similar to CSA but AZA not effective

**CONCLUSION:** 8 wk course of CYC or Chlor or prolonged CSA reduce risk of relapsing SSNS v steroids alone

Hodson et al, Cochrane database Syst Rev 2008

### Rituximab in Adults with SD/FR-MCD

- 17 adults SD/FR-MCD, failed CYC, CSA, MMF, etc
- After 1 course, 11 (65%) pts had sustained remission at 27 mo while 6 pts relapsed after 11 mo FU.
- Relapse assoc. with increased B-cell cts, but responded to retreatment.
- Relapse rate fell from 1.3 to 0.16 per yr
- Steroids/immunosuppression DCed in 70% of pts
- RTX leads to remission in adults with SD/FR-MCD, allowing withdrawal of steroids and immuno-therapy

Munyentwali et al. KI 2013
(Bruchfield et al: NDT 2014; Ruggenenti et al JASN 2014)

### Long-term Outcome in Adult MCD

<table>
<thead>
<tr>
<th>Follow-up (mo)</th>
<th>Remission</th>
<th>Complete</th>
<th>Partial</th>
<th>Nephrotic</th>
<th>ESRD</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nolasco KI 1986</td>
<td>91±63</td>
<td>66%</td>
<td>11%</td>
<td>6%</td>
<td>1%</td>
<td>17%</td>
</tr>
<tr>
<td>Korbet AJN 1988</td>
<td>64±47</td>
<td>77%</td>
<td>12%</td>
<td>20%</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td>Fujimoto AJKD 1991</td>
<td>46±29</td>
<td>66%</td>
<td>11%</td>
<td>6%</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Mak NDT 1996</td>
<td>169</td>
<td>94%</td>
<td>7%</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Follow-up: 91±63 mo, Remission 66%, Complete 3%, Nephrotic 6%, ESRD 1%, Died 17%

### Treatment of iMCD in Nephrotic Adults: KDIGO

1. Prednisone 1 mg/kg/d (max 80 mg) or 2 mg/kg qod (max120 mg) for a min of 4 wks if CR is achieved, and max of 16 wks if no CR.
2. In pts who remit, taper over 6 mo.
3. Contraindications to steroids (DM, obesity, psychiatric conditions, severe osteoporosis), use oral CYC or CNIs.
4. Infrequent relapsers- use the same initial dose of steroids until in CR and then taper over 2 mo.
5. FR/SD pts- oral CYC 2-2.5 mg/kg/d for 8 wks.

-CNIs in pts who have relapsed despite CYC or to preserve fertility.
-MMF 750-1000 mg BID in pts intolerant of steroids, CYC or CNIs.

KDIGO, KI Suppl. 2012; 2:139-274
FOCAL SEGMENTAL GLOMERULOSCLEROSIS

FSGS is the Most Common Cause of Nephrotic Syndrome in African American Adults

Korbet et al, AJKD 1996

Percent of Patients

MCD | FSGS | MGN | MPGN | Other
---|---|---|---|---
Black | 14% | 57% | 36% | 2% | 15%
White | 20% | 23% | 6% | 2% |

FSGS the Most Common Cause of GN Related ESRD in US in Black and White Pts

Kitiyakara, Kopp et al, AJKD 2004

“Pathogenic” Classification of FSGS

- Primary alterations of GEC
  - Primary FSGS
  - HIV-associated nephropathy
  - Parvovirus B19
  - Heroin-associated nephropathy
  - Parvovirus, Li, Anabolic steroids
  - Familial FSGS
  - Sporadic genetic mutations

- Reduced nephron mass / glomerular adaptation
  - Nephrectomy
  - Reflux nephropathy
  - Obesity related glomerulosclerosis

- Secondary to focal proliferative glomerulonephritis

Viral

Drugs

Genetic
Cardiotrophin-like Cytokine-1 (CLC1) is a Candidate for the FSGS Permeability Factor

Savin et al, ASN 2008, CJASN 2010

Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis - suPAR

Chang Li Wei1, Saheb El Hindy1,2, Jing Li1,2, Alexia Fermon1,2,3, Nelson Gove1, Junichiro Sagashima4, Dosy Magne1,3, S Ananth Karunamuni1,4, Thi Kim Yap5, Mona Saleri5, Qinglin Zhang6, Birte Silboe6, Ahmad Chaudhri3, Priya Duttagupta5,6, Eduardo Salgado7, Armando Torres7, Mario Saliba1, Malko M Narwal7, Franz Scherf7, Christian Mortal1,4, Verdict Schwenger2,3, Martin Zeier2,3, Virgo Gupta3, David Roth5,6, Maria Pia Rastold4, George Burke5, Philipp Ritz1,6, R. Jochen Reiter1,6

Nature Medicine, 17:952, 2011

MYH9 and APOL1 in FSGS and HIVAN

- MYH9 variant common in AA (60% of alleles) vs 4% in European Americans
- May explain excess risk for FSGS and HIVAN in AA

Nature Genetics, 40:1175, 2008

Presenting Features in Idiopathic FSGS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic</td>
<td>90%</td>
<td>70%</td>
</tr>
<tr>
<td>Male</td>
<td>55%</td>
<td>60%</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>20%</td>
<td>30%</td>
</tr>
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Sethi, Glassock & Fervenza, NDT 2014

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Missence mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene

Renal Survival in Adult FSGS Based on Proteinuria


Renal Survival in Nephrotic Adults with FSGS Based on Remission Status

Troyanov, Cattran, et al for the Toronto GN Registry, JASN 2005

Treatment in Primary FSGS

Proteinuric patient with Primary FSGS

ACEi / ARB, Statins & BP control

Non-nephrotic

Follow

Nephrotic

Begin immunosuppressive therapy

"Permeability factor"

Immunosuppressive Therapy

Mature Podocyte

Foot process effacement

Cellular lesion

Segmental scar

Proteinuria

Renal insufficiency
Direct effects of dexamethasone on human podocytes
C.Y. Xing1,2, MA Salem1, RJ Coward1, LN1, IL Withersden1 and PW Mathieson1

The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A
Christian Endo1,2, Mary Donnelly1,2, Sandra Merscher-Gomez1,2, Soon Hye Chung1,2, Stefan Franz1,2, Jacqueline Delguardo1,2, Jae-Ming Chung1,2, Hoew Young Cheu1, Kirk N. Campbell1,2, Joong Yoh Kim1,2, Jens Reiser1,2 & Peter Meade1,2

Response to Steroids in Adult FSGS
High Dose Steroids

<table>
<thead>
<tr>
<th>Researcher</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal: 1993</td>
<td>32%</td>
<td>26%</td>
</tr>
<tr>
<td>Cattran: 1998</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Ponticelli: 1999</td>
<td>40%</td>
<td>19%</td>
</tr>
<tr>
<td>Chun/ Korbet: 2004</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td>Stirling: 2005</td>
<td>37%</td>
<td>29%</td>
</tr>
</tbody>
</table>

0% 10% 20% 30% 40% 50% 60% 70% 80%

Complete Remission Partial Remission

Time to Remission in FSGS

Median Time:
Rydel: 3.7
Cattran: 4
Ponticelli: 5

Jafry et al., NDT 2012

Time to Remission in FSGS

Korbet, Unpublished
Response to Steroid Therapy in FSGS

<table>
<thead>
<tr>
<th>Steroid Duration</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16 weeks</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;16 weeks</td>
<td>61%</td>
</tr>
</tbody>
</table>

Ponticelli, AJKD 1999

Steroid Resistance in Adults:

Persistence of the nephrotic syndrome after 4 months of prednisone at a dose of 1 mg/kg/day.

Meyrier et al, Kidney Int 1994

Classification of Focal Segmental Glomerulosclerosis

- FSGS (NOS)
- Perihilar variant
- Cellular variant
- Tip variant
- Collapsing variant

D’Agati: Seminars in Nephrol 2003

Features and Prognosis in FSGS Variants

<table>
<thead>
<tr>
<th>Lesion</th>
<th>NOS</th>
<th>Collapsing</th>
<th>Tip</th>
<th>Perihilar</th>
<th>Cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>83</td>
<td>22</td>
<td>34</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Black</td>
<td>43%</td>
<td>91%</td>
<td>15%</td>
<td>29%</td>
<td>33%</td>
</tr>
<tr>
<td>Nephrotic</td>
<td>67%</td>
<td>83%</td>
<td>88%</td>
<td>55%</td>
<td>75%</td>
</tr>
<tr>
<td>SCr (mg/dl)</td>
<td>2.1</td>
<td>3.1</td>
<td>1.5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>5.5</td>
<td>10</td>
<td>9.7</td>
<td>4.4</td>
<td>16</td>
</tr>
<tr>
<td>Remission</td>
<td>16%</td>
<td>18%</td>
<td>53%</td>
<td>19%</td>
<td>24%</td>
</tr>
<tr>
<td>Complete R</td>
<td>13%</td>
<td>14%</td>
<td>50%</td>
<td>10%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Thomas, Falk et al, KI 2006
Course in FSGS Based on Variants

Features and Prognosis in FSGS Variants

Collapsing/Cellular FSGS

The Collapsing lesion of FSGS
### Response to Initial Therapy in FSGS

<table>
<thead>
<tr>
<th></th>
<th>&lt;20% Collapsing</th>
<th>≥20% Collapsing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Remission</td>
<td>12 (92%)*</td>
<td>4 (33%)</td>
</tr>
</tbody>
</table>

*p = 0.008

Chun, Korbet et al., JASN 2004

### Tip variant

Stokes, D'Agati et al., KI 2004

### Glomerular Tip Lesion in Nephrotic FSGS

<table>
<thead>
<tr>
<th></th>
<th>Chun et al</th>
<th>Stokes et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated (n)</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Remission</td>
<td>7 (78%)</td>
<td>21 (72%)</td>
</tr>
<tr>
<td>Complete</td>
<td>5 (56%)</td>
<td>17 (58%)</td>
</tr>
<tr>
<td>Partial</td>
<td>2 (22%)</td>
<td>4 (14%)</td>
</tr>
</tbody>
</table>

Chun, Korbet, et al., JASN 2004
Stokes, D'Agati et al., KI 2004

### Response to Treatment in Nephrotic FSGS

<table>
<thead>
<tr>
<th></th>
<th>Classic</th>
<th>Collapsing</th>
<th>Tip</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>Treated</td>
<td>17 (47%)</td>
<td>25 (63%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Remission</td>
<td>9 (53%)</td>
<td>16 (64%)</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>Complete</td>
<td>6 (35%)</td>
<td>6 (24%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Partial</td>
<td>3 (18%)</td>
<td>10 (40%)</td>
<td>2 (22%)</td>
</tr>
</tbody>
</table>

Chun, Korbet, et al., JASN 2004
Response to treatment in Idiopathic Nephrotic FSGS: Children vs Adults
Pei, Am J Med 1987

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>44%</td>
<td>39%</td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td>15%</td>
</tr>
</tbody>
</table>

Relapse after Partial Remission in FSGS
Troyanov, Caltrant, et al for the Toronto GN Registry, JASN 2005

Treatment Options in FSGS
- Steroids
- Cytotoxic agents
  - Cyclophosphamide
  - Chlorambucil
  - Mycophenolate mofetil
- Calcineurin inhibitors
  - Cyclosporine
  - Tacrolimus

Response to Cytotoxic and CSA Therapy Based on Initial Steroid Response in FSGS

<table>
<thead>
<tr>
<th>Initial response to steroids</th>
<th>N</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-responsive</td>
<td>43</td>
<td>22 (51%)</td>
<td>10 (23%)</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>Steroid-resistant</td>
<td>185</td>
<td>31 (17%)</td>
<td>27 (15%)</td>
<td>127 (69%)</td>
</tr>
<tr>
<td>Cyclosporine A therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-responsive</td>
<td>15</td>
<td>11 (73%)</td>
<td>1 (7%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Steroid-resistant</td>
<td>281</td>
<td>82 (29%)</td>
<td>61 (22%)</td>
<td>138 (49%)</td>
</tr>
</tbody>
</table>

Korbet, KI 2001
Randomized Placebo Controlled Trial of CSA in Adult Steroid-Resistant FSGS

- 49 steroid-resistant FSGS pts (>8 wks, >1 mg/kg/d)
- All received prednisone 0.15 mg/kg/d
- CSA dose: 3.5 mg/kg/d in 2 divided doses
- 12 hr trough: 125 - 225 ug/L
- Treated for 6 months and tapered over 1 month

Cattran and the North American Nephrotic Study Group, KI 1999

Complete Rem: 12%
Partial Rem: 57%
CSA: 26 pts
Placebo: 23 pts

CSA in FSGS: Remission

Guidelines for the use of CSA in FSGS

- After remission, reduce by 0.5 mg/kg/mo to 2.5 mg/kg/d and if proteinuria returns increase to previous dose
- Attempt to taper off CSA after 1 to 2 years

Ponticelli, ASN Toronto 2000
Tacrolimus in CSA-dependent or -resistant FSGS: Uncontrolled Prospective Study

- 25 adults with steroid-resistant FSGS
  - tacrolimus for 6 months
- Remission rate:
  - CSA-responsive: 83%
  - CSA-resistant: 15%
- Mean time to remission was 4 months
- Relapse rate 76%, within 1-4 months
- May be an alternative to CSA with similar profile

Segarra et al: Nephrol Dial Transplant 2002
(Ramachandran et al: Nephrol Dial Transplant 2014)

MMF in Steroid-Resistant Adult FSGS

18 nephrotic adults, prospective study
MMF dose- 1750 mg/d, duration- 8 months

<table>
<thead>
<tr>
<th>Week</th>
<th>Partial Remission</th>
<th>Proteinuria Response</th>
<th>No-Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>33%</td>
<td>11%</td>
<td>56%</td>
</tr>
<tr>
<td>78</td>
<td>28%</td>
<td>72%</td>
<td></td>
</tr>
</tbody>
</table>

Catran et al, Clin Nephrol 2004

NIH Clinical Trial: CSA vs MMF in SR-FSGS

- Prospective, randomized, controlled trial, 52 wks
- Steroid resistant FSGS between 2 and 40 yrs old
- CSA vs MMF + pulse steroids for 12 months
- All pts on ACEi and alternate day prednisone
- Primary Objective: to determine if MMF + Pulse steroids is superior to CSA in inducing remission

Final results: negative study!

CR/PR: 44% CSA, 33% MMF
(Gipson et al, KI 2011)

CSA vs MMF in SR-FSGS: FSGS Variants

D’Agati et al, CJASN 2013
Other Treatment Options in FSGS

- Plasmapheresis / Protein adsorption
- Rituximab
- ACTH (low response rate in SR pts: Hogan et al CJASN 2014)
- Pirfenidone (anti fibrotic agent)
- Fresolimumab (anti-TGF-beta ab)
- CSA+MMF (no adv in CSA-R pts: Segarra et al Nefrologia 2011)

FSGS Associated with Anabolic Androgenic Steroid Use in Bodybuilders

- 10 pts (W-6, H-4), long-term AAS use, BMI 35 kg/m²
- UPro-10 g/d (1-26 g/d), 5 pts with NS
- SCr- 3 mg/dl (1.3-8)
- FSGS-9 and/or glomerulomegaly-5
  - Perihilar-4, collapsing-3, 7 had >40% interstitial fibrosis
- Follow-up in 8 pts of 2 yrs
  - 1 progressed to ESRD rapidly
  - Off AAS, 7 had stable/improved SCr and UPro with ACEi
- FSGS may result from post-adaptive glomerular changes due to increased BMI and toxic effects of AAS

Obesity-related FSGS

<table>
<thead>
<tr>
<th>ORG</th>
<th>I-FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>71</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42</td>
</tr>
<tr>
<td>Older age (yrs):</td>
<td>43</td>
</tr>
<tr>
<td>White:</td>
<td>75%</td>
</tr>
<tr>
<td>Proteinuria &gt;3.5 g/d:</td>
<td>48%</td>
</tr>
<tr>
<td>Nephrotic syndrome:</td>
<td>6%</td>
</tr>
<tr>
<td>Glomerulomegaly:</td>
<td>100%</td>
</tr>
<tr>
<td>Extent foot process fusion:</td>
<td>40%</td>
</tr>
</tbody>
</table>

Kambham et al, KI 2001

Herlitz, D’Agati al, ASN 09, PO 163
Treatment of iFSGS in Nephrotic Adults: KDIGO

[2] Prednisone 1 mg/kg/d (max 80 mg) or 2 mg/kg qod for a min of 4 wks and a max of 16 wks or until CR, whichever is first.
[3] In pts with CR, taper steroids over of 6 mo.
[4] Contraindications to steroids- consider CNI as initial therapy.
[5] Treat relapses in FSGS as in relapsing MCD.
[6] Steroid-resistant FSGS: CSA 3-5 mg/kg/d in divided doses for 4-6 mo. If there is PR/CR continue for 12 mo, then slow taper.

MEMBRANOUS NEPHROPATHY

Secondary Membranous Glomerulonephritis

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>729 77%</td>
</tr>
<tr>
<td>Secondary</td>
<td>214 23%</td>
</tr>
<tr>
<td>Drugs</td>
<td>62 7%</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>49 5%</td>
</tr>
<tr>
<td>SLE</td>
<td>45 5%</td>
</tr>
<tr>
<td>Infections</td>
<td>31 3%</td>
</tr>
<tr>
<td>Other</td>
<td>27 3%</td>
</tr>
</tbody>
</table>

Anti-PLA2R in iMGN

Sensitivity 75% Specificity 100%
Overall Correlation of Proteinuria with anti-PLA2R in Antibody-Positive Patients

-71% PLA2R Ab +
-Ab declined in 68% of pts
-2 yr remission rate 88% when the Ab declined vs 33% when it didn’t

Anti-PLA2R Ab Correlates with Disease Activity

Anti-PLA2R Ab Level Predicts Outcome

Hofstra et al, CJASN 2011

Beck & Salant, KI 2010

Beck et al, ASN 09, Hofstra et al, CJASN 2011
Anti-PLA2R Ab Level Predicts Outcome

- Spontaneous remissions (26%) were rarely seen in patients with high titers (4% vs 38%)
- Time to remission with treatment (72%) was 5 mo in pts with lowest titers and 10 mo in those with the highest titers.

Renal Survival in iMGN

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td></td>
<td>32</td>
<td>23</td>
<td>12</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td></td>
<td>53</td>
<td>42</td>
<td>31</td>
<td>24</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>287</td>
<td></td>
<td>210</td>
<td>143</td>
<td>98</td>
<td>61</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

Polanco et al., JASN 2010

Spontaneous Remission in Nephrotic iMGN

<table>
<thead>
<tr>
<th>Baseline Proteinuria (g/24 h)</th>
<th>n</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
<th>CR + PR Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 - 8</td>
<td>186</td>
<td>17%</td>
<td>20%</td>
<td>37%</td>
</tr>
<tr>
<td>8 - 12</td>
<td>91</td>
<td>14%</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>&gt;12</td>
<td>51</td>
<td>14%</td>
<td>8%</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>328</td>
<td>16%</td>
<td>16%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Only 6% of Pts had a relapse of NS over 91 mo of FU

Polanco et al., JASN 2010
**Spontaneous Remission in Nephrotic iMGN**

Polanco et al, JASN 2010

---

**Spontaneous Remission in Nephrotic iMGN: Recommendations**

- Monitor all pts closely on ACEi/ARBs for 12-18 mo
  - Provided SCr normal and UPro declines
- >50% ↓ UPro predicts spont-remission (HR: 13)
- Start immunosuppressive therapy:
  - if renal function deteriorates
  - in pts without improvement in UPro

---

**Benefit of Partial Remission in iMGN**

Polanco et al, JASN 2010

---

**Predicting Progressive Renal Disease in iMGN**

Cattran, KI 2001

<table>
<thead>
<tr>
<th>Proteinuria (g/d)</th>
<th>6 month persistent proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Sensitivity 93%</td>
<td>81%</td>
</tr>
<tr>
<td>Specificity 38%</td>
<td>67%</td>
</tr>
<tr>
<td>PPV 34%</td>
<td>46%</td>
</tr>
<tr>
<td>NPV 94%</td>
<td>91%</td>
</tr>
<tr>
<td>Accuracy 52%</td>
<td>71%</td>
</tr>
</tbody>
</table>

---

**Benefit of Partial Remission in iMGN**

Troyanov, Cattran et al, KI 2004

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**Predicting Progressive Renal Disease in iMGN**

Cattran, KI 2001
Risk of Progression Categories

Low risk (<5% chance of progression)
- **Laboratory**
  - Normal Function
  - Proteinuria < 4 g/d
- **Time**
  - 6/12

Medium risk
- Normal function
- Persistent proteinuria ≥4 <8 g/d
- **Time**
  - 6/12

High risk
- Abnormal function and/or Persistent proteinuria ≥8 g/d
- **Time**
  - 6/12

Results of Controlled Trials with Oral Prednisone in iMGN= NO BENEFIT

<table>
<thead>
<tr>
<th></th>
<th>Coggins</th>
<th>Catran</th>
<th>Cameron</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Tx C</td>
<td>Tx C</td>
<td>Tx C</td>
</tr>
<tr>
<td>34</td>
<td>38</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>12% 11%</td>
<td>24% 42%</td>
<td>19% 14%</td>
</tr>
<tr>
<td>Complete R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial R</td>
<td>23% 8%</td>
<td>37% 30%</td>
<td></td>
</tr>
<tr>
<td>Total R</td>
<td>35% 19%</td>
<td>61% 72%</td>
<td></td>
</tr>
<tr>
<td>F-Up (mos)</td>
<td>36</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>3% 26%*</td>
<td>4% 5%</td>
<td>21% 30%</td>
</tr>
</tbody>
</table>

Coggins, NEJM 1979
125 mg qod for 2 months

Catran, NEJM 1989
45 mg/m2 qod (80 mg) for 6 months

Cameron, QJM 1990
125 mg qod for 2 months

Treatment of iMGN with Alkylating Agents

“Ponticelli Protocol”

Month 1: Methylprednisolone 1g IV for 3 days, then prednisone 0.5 mg/kg/d for 27 days

Month 2: Chlorambucil 0.2 mg/kg/day for 30 days, or Cyclophosphamide 2 mg/kg/d

Cycle 3 times for a total of 6 months of therapy
10-yr Follow of Ponticelli Protocol in iMGN
(Remission Rate)

Ponticelli, KI 1995

10-yr Follow of Ponticelli Protocol in iMGN
(Survival without ESRD)

Ponticelli, KI 1995

No Difference in Outcome for Chlor vs CYC using Ponticelli Protocol in iMGN

Ponticelli, KI 1995

Cyclosporine in Steroid-resistant Nephrotic iMGN
Remission in Proteinuria

Cattran et al, KI 2001

Probability of Remission

Probability of Relapse

Ponticelli et al, JASN 1998

CSA: 28 pts
Placebo: 23 pts

P= 0.003
Prospective placebo controlled trial
Decline in CrCl of ≥8 ml/min over 12 mo
Proteinuria of >3.5 g/24h
3.5 mg/kg/day for 12 mos
12h trough of 110 - 170 mcg/L

<table>
<thead>
<tr>
<th></th>
<th>CSA (n=89)</th>
<th>Placebo (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>11.5±3</td>
<td>12.8±4</td>
</tr>
<tr>
<td>3 months</td>
<td>7±4*</td>
<td>13.5±9</td>
</tr>
<tr>
<td>12 months</td>
<td>8±7</td>
<td>11±5</td>
</tr>
<tr>
<td>Last Follow-up</td>
<td>4.5±4*</td>
<td>9.2±5</td>
</tr>
</tbody>
</table>

The improvement in renal function persisted for up to 40 months after CSA was discontinued
At last follow-up (21-50 mo post-trial), ESRD in 12% of CSA pts vs. 50% of placebo pts

The improvement in renal function persisted for up to 40 months after CSA was discontinued
At last follow-up (21-50 mo post-trial), ESRD in 12% of CSA pts vs. 50% of placebo pts

Similar findings using Tacrolimus- Praga et al: KI 2007
MMF vs CYC in Idiopathic MGN

- 32 case and 32 matched historic controls
- High risk: SCr >1.5 mg/dl and UPro/Cr: 5-14 g/g
- No immunosuppression in past 6 mos, all on ACEi
- MP 1 g IV for 3 days on mos 1, 3, and 5 (all pts)
- Prednisone 0.5 mg/kg QOD for 6 mos (all pts)
- MMF 1 g BID or CYC 1.5 mg/kg/d for 12 mos
- Outcomes based on UPro/Cr ratio (g/g):
  - CR: ≤0.18
  - PR: 0.19 - 1.77
  - PP: >1.77 - <3.1
  - NS: ≥3.1

Branten et al: AJKD 2007

Cumulative Remission Rate in MGN

MMF vs CYC in Idiopathic MGN

- Complication rates similar
- MMF was not as effective as CYC

Branten et al: AJKD 2007
Rituximab in Nephrotic iMGN
- 100 consecutive cases with persistent NS on ACEi
- 68% 1st line therapy, 32% 2nd line therapy
- Treated with 1-4 doses
- Remission- 65% [CR-27%, PR-38%]

ACTH in Nephrotic iMGN
- N= 20 nephrotic pts on ACEi/ARBs
- ACTH 80 units BIW x 12 wks
- UPro decreased from 9 to 4 g/d
- >50% decrease in UPro in 65% of pts

Treatment of iMGN in Nephrotic Adults: KDIGO

[1] Exclude secondary causes in all cases of iMGN.

[2] Start therapy ONLY in pts with NS AND with at least ONE of the following:
   • UPro persistently >4 g/d despite ACEi/ARBs for 6 mo;
   • severe or life-threatening symptoms from the NS;
   • SCr has risen by 30% over 6-12 mo but eGFR >30.

[3] Pts with SCr persistently >3.5 mg/dl or eGFR <30 should NOT be exposed to immunosuppressive therapy.

   - CYC daily can be used but greater risk when given for >6 mo.

[5] Conservative mgt for 6 mo post initial regimen if no response, unless kidney function is deteriorating.

[6] CSA or tacrolimus can be an alternative for initial therapy
   - use for at least 6 mo and discontinue if no PR/CR.
   - in PR/CR pts reduce dose q 4-8 wks to 50% of starting dose and continue for 12 mo and monitor blood levels regularly.
Treatment of iMGN in Nephrotic Adults: KDIGO

[7] The use of steroids alone, MMF, Rituximab or ACTH is NOT recommended for INITIAL THERAPY.

[8] Treatment in pts resistant to initial therapy: CNI or CYC.

[9] Treating relapses: use therapy that led to initial remission. -if a 6 mo cyclical course of steroid/CYC was used, repeat only once for treatment of a relapse.

Prophylactic anticoagulation:

“We suggest that pts with iMGN and nephrotic syndrome with Salb <2.5 g/dl and additional risks for thrombosis be considered for prophylactic anticoagulation using warfarin”.

Prevention of Venous Thromboembolism in NS

- N= 143 (MGN, MCD, FSGS), 3 yrs follow-up
- NO VTE in pts on prophylaxis for at least 1 week
- 2/143 (1.4%) VTE within 1 week of starting prophylaxis

Venous Thromboembolism in iMGN

7.2% (65/898) of pts had Thromboembolic events

OR >2 for Salb <2.8 g/dl

<table>
<thead>
<tr>
<th>Serum Albumin (g/dl)</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range &gt;3.0</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 to &lt;3.0</td>
<td>2.53</td>
<td>0.55, 4.36</td>
<td>0.32</td>
</tr>
<tr>
<td>2.0 to &lt;2.5</td>
<td>3.31</td>
<td>0.31, 4.62</td>
<td>0.77</td>
</tr>
<tr>
<td>2.0 to &lt;2.5</td>
<td>3.14</td>
<td>1.46, 13.77</td>
<td>0.01</td>
</tr>
<tr>
<td>2.0 to &lt;2.0</td>
<td>4.50</td>
<td>1.25, 15.64</td>
<td>0.02</td>
</tr>
<tr>
<td>2.0 to &lt;2.0</td>
<td>2.52</td>
<td>1.17, 5.47</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Lionaki, Falk, Catrgran, Nachman et al: JASN 2012
Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy


(www.gntools.com)