MINIMAL CHANGE DISEASE
FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

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Disclosure of Interests

• No relevant disclosures
Minimal change disease/steroid sensitive nephrotic syndrome in children
Duration of prednisone for the initial episode of childhood SSNS:
Number with FRNS at 1-2 years*

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>3 months or more</th>
<th>2 months therapy</th>
<th>Risk Ratio</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Norero 1996</td>
<td>3</td>
<td>29</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Ueda 1988</td>
<td>3</td>
<td>17</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>APN 1993</td>
<td>6</td>
<td>34</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>Bagga 1999</td>
<td>7</td>
<td>22</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Jayantha 2002a</td>
<td>8</td>
<td>48</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>Yoshikawa 2014</td>
<td>45</td>
<td>122</td>
<td>48</td>
<td>124</td>
</tr>
<tr>
<td>PREDNOS Study 2017</td>
<td>59</td>
<td>113</td>
<td>54</td>
<td>109</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>385</td>
<td>419</td>
<td>100.0%</td>
<td>0.79 [0.58, 1.07]</td>
</tr>
</tbody>
</table>

Total events: 131, 165

Heterogeneity: Tau² = 0.06; Chi² = 10.57, df = 6 (P = 0.10); I² = 43%
Test for overall effect: Z = 1.53 (P = 0.12)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>5 or 6 months</th>
<th>Three months</th>
<th>Risk Ratio</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Mishra 2012</td>
<td>1</td>
<td>37</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>Sharma 2000</td>
<td>8</td>
<td>70</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>Hiraoka 2003</td>
<td>10</td>
<td>36</td>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>Sinha 2014</td>
<td>36</td>
<td>92</td>
<td>35</td>
<td>89</td>
</tr>
<tr>
<td>Teeninga 2013</td>
<td>38</td>
<td>64</td>
<td>31</td>
<td>62</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>299</td>
<td>292</td>
<td>100.0%</td>
<td>0.78 [0.50, 1.22]</td>
</tr>
</tbody>
</table>

Total events: 93, 106

Heterogeneity: Tau² = 0.15; Chi² = 12.05, df = 4 (P = 0.02); I² = 67%
Test for overall effect: Z = 1.07 (P = 0.28)

*Hahn D et al. CDSR 2015, CD001533
Prednisone + steroid-sparing agents to prolong time to first relapse in children with SSNS

- **Azithromycin (Zhang 2014). RCT**
  - Intervention: Azithromycin + prednisone (106)
  - Comparator: Prednisone (105)
  - Outcome at 6 months:
    - No difference in number with relapse or FRNS at 6 months

- **INTENT study (EudraCT 2014-001991-76. N=400/340; Germany). RCT**
  - Intervention: Prednisone till remission, then MMF for rest of 12 week induction period. Alternate day prednisone for 2 weeks
  - Comparator: 6 weeks daily and 6 weeks alternate day prednisone
  - Outcome: First relapse within 24 months
  - 110 recruited to date. Completion expected 2020 (Dr Marcus Benz)

- **NEPHROVIR3 study (NCT02818738. N 156: France). RCT**
  - Intervention: Levamisole for 6 months after first remission
  - Comparator: Placebo for 6 months after first remission
  - Recruitment not started. Completion expected 2020
Steroid regimens to prevent relapse in children with SSNS

- Yadav et al 2016 (CTRI/2012/12/003194; Pediatric Nephrology (2016) 31:1752)
  - Open label RCT enrolling 62 children aged 1-16 years with FRNS without steroid toxicity
  - Intervention: Daily prednisone 0.2-0.3 mg/kg/day for 12 months
  - Comparator: Alternate day prednisone 0.5–0.7 mg/kg/day for 12 months
Steroid regimens to prevent relapse in children with SSNS

• Reduced prednisone schedule vs standard schedule
  – RESTERN study 2017 (EudraCT - 2016-002430-76; BMJ Open 2017;7:e018148)
    • Double-blind RCT enrolling 144 children aged 1-18 years with relapse of SSNS
    • Intervention: Reduced prednisone schedule (daily till remission, alt day for 2 weeks)
    • Comparator: Standard prednisone schedule (daily till remission, alt day for 6 weeks)
    • Outcome: Time to next relapse

• Increased dose of prednisone to prevent relapse with infections
  – Abeyagunawardena 2017 (Pediatric Nephrology 32: 1377-1382, 2017)
    • Cross-over study (48 patients/33 completed) showed fewer relapses in children with FRNS (not on prednisone) given daily prednisone at onset of infection compared with placebo
  – PREDNOS 2 Study (EudraCT – 2012-003476-39)
    • RCT comparing 6 days of prednisone with placebo in children with FRNS & URTI
    • Results awaited. 295/360 patients enrolled to date (data from N. Webb)
Levamisole reduces the risk of relapse in children with FRNS

Eudra CT 2005-005745-18
The relative efficacies of CNIs and MMF in children with FRNS


MMF vs TAC
(non-randomised comparator study)
Should rituximab be used as first line steroid-sparing agent in children with SDNS?: Efficacy

Should rituximab be used as first line steroid-sparing agent in children with SDNS?: Adverse effects

Reported in nephrotic syndrome
- Infusion reactions
- Fever, skin rash, arthritis
- Hypersensitivity in 2nd courses
- Hypogammaglobulinaemia
- Infections
- Fulminant myocarditis
- Pulmonary fibrosis
- Pneumocystitis pneumonia
- Immune-mediated ulcerative colitis
- Agranulocytosis

Reported in other conditions
- Reactivation of Hep B virus
- Progressive multifocal leucodystrophy
- Secondary malignancies
- Death due to infections
Minimal change disease in adults
Tacrolimus for adults with new-onset MCD

- Li et al 2017 (JASN 28: 1286-1295, 2017; ChiCTR-TRC-11001454)
  - Intervention (N=63): 10 days of IV MP, then tacrolimus for 36 week with FU to 64 weeks
  - Comparator (N=56): 10 days of IV MP, then prednisone for 36 weeks with FU to 64 weeks
  - 1\textsuperscript{er} outcome: remission at 12 wks, Tac 52/56 (93\%) vs pred 51/53 (96\%)

\textbf{2\textsuperscript{er} outcome: Relapse}
No relapse: TAC 55\%; Pred 51\%

\textbf{2\textsuperscript{er} outcome: SAE}
TAC 2; Pred 7
Other studies of steroid-sparing agents in adults with MCD*

Table 3. Published experience for the treatment of steroid-resistant, SD, and FR MCD in adults

<table>
<thead>
<tr>
<th>Medication</th>
<th>Evidence</th>
<th>Regimen</th>
<th>Remission Rates</th>
<th>Relapse Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SR*  SD  FR  SR*  SD  FR</td>
<td></td>
</tr>
<tr>
<td>Oral CYC</td>
<td>Observational series; one RCT in adults</td>
<td>2–2.5 mg/kg per d×8 wk</td>
<td>50%–80% 50%–80% 50%–80%</td>
<td>50% 25%–56% 25%–56%</td>
</tr>
<tr>
<td>iv CYC</td>
<td>Two small RCTs in adults</td>
<td>750 mg/m² per mo×6 mo + steroids</td>
<td>50% 77% NA</td>
<td>14% 40% NA</td>
</tr>
<tr>
<td>Cyclosporine ± prednisone</td>
<td>Large observational series data; one small RCT in children and one RCT in adults</td>
<td>3–5 mg/kg per d in divided dose×1–2 yr</td>
<td>45%–92% 45%–92% 45%–92%</td>
<td>NA 62%–75% 62%–75%</td>
</tr>
<tr>
<td>Tacrolimus ± prednisone</td>
<td>Small observational series; two small RCTs in adults</td>
<td>0.05–0.1 mg/kg per d in divided dose×1–2 yr</td>
<td>79%–100% 91%–100% NA</td>
<td>40% 50% NA</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Small observational series; one small RCT in children</td>
<td>1–2 g/d in divided dose</td>
<td>25% 80%–100% 58%</td>
<td>NA 20%–50% 20%–50%</td>
</tr>
</tbody>
</table>

*Hogan & Radhakrishnan JASN 24: 702-711, 2013
Observational studies of steroid sparing agents in relapsing MCD in adults

- **Sandoval 2017**: Mycophenolate mofetil/sodium (MF) + prednisone
  - Report of 29 adults with FRNS/SDNS
  - Remission in 27 (25 CR, 2 PR)
  - Medication ceased after 12-49 months in 20; 9 relapsed & achieved continued remission with further pred/MF

- **Guitard 2014**: Rituximab
  - Report of 41 adults with SDNS; variable dosing; 21 in remission & 20 in relapse
  - Remission in 32 (25 CR, 7 PR); 18 (5 PR) relapsed after 3-36 mths & 17 re-treated with remission in all (13 CR, 4 PR)

- **Ruggenenti 2014**: Rituximab
  - Report of 20 adults & 10 children with FRNS/SDNS; 1 or 2 doses
  - At one year, all in remission & 15 never relapsed
Investigational treatment for MCD

- Angiopoietin-like protein 4 (Angptl4) is a secretory glycoprotein that is essential for maintenance of the negative charge of GBM.
- Glomerular expression of Angptl4 is glucocorticoid sensitive
- Rats overexpressing Angptl4 develop nephrotic proteinuria, loss of GBM charge and foot process effacement
- Podocyte-secreted hyposialylated Angptl4 appears to mediate proteinuria in MCD
- N-acetyl-D-manosamine (ManNAc) converts hyposialylated Angptl4 to sialylated protein and it reverses proteinuria in experimental models
- Phase 1 study (NCT02639260) of ManNAc commenced 2015; will enrol 12 adult subjects with MCD, FSGS, MN in relapse
FSGS/SRNS in children and adults
The six forms of FSGS: prevalence among US adults*

Genetic FSGS: Studies of causative mutations in 187 children with SRNS/CNS*

- Single gene mutations identified in 26% of 187 children aged < 19 years in 17/53 known SRNS genes.
- Mutations in 59% (13/22) familial SRNS and 22% (36/164) non-familial SRNS.

FSGS in African Americans associated with mutations in \textit{APOL1} (encodes apolipoprotein L1)

- NIH study*
  - FSGS in African Americans associated with homozygous or compound heterozygotes of G1 and G2 variants of \textit{APOL1} (OR 16.9 (95% CI 11–26.5))
  - Two renal risk alleles associated with earlier age of onset of FSGS & faster progression to ESKD
  - \textbf{BUT} – no difference in response to corticosteroids (8 weeks)
    - 29\% (2 renal risk alleles)
    - 33\% (0-1 risk alleles)

- FSGS-CT**
  - 94/138 genotyped for \textit{APOL1} renal risk alleles; 27 had 2 risk alleles
  - Two risk alleles associated with lower kidney function, more rapid progression to ESKD, more glomerulosclerosis and interstitial fibrosis
  - \textbf{BUT} – no difference between 2 renal risk alleles and 0-1 renal risk alleles in response to treatment (cyclosporin, MMF, dexamethasone)

Differentiation between primary and secondary (adaptive) FSGS*

Table 2. Clinical and histological characteristics of primary versus secondary FSGS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Primary FSGS</th>
<th>Secondary FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Acute onset</td>
<td>Proteinuria develops gradually</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&lt;3.5 g/dL b</td>
<td>≥3.5 g/dL</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>≥3.5 g/24 h</td>
<td>Variable but can be &gt;3.5 g/24 h</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Edema</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Glomerulomegaly</td>
<td>Less common (30%)</td>
<td>Common (70%)</td>
</tr>
<tr>
<td>Foot process effacement</td>
<td>Diffuse (&gt;80%)</td>
<td>Segmental (&lt;50%)</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Dependent on response to</td>
<td>Slowly</td>
</tr>
<tr>
<td></td>
<td>immunosuppressive therapy</td>
<td>progressive</td>
</tr>
</tbody>
</table>

*Excluding collapsing FSGS.

b Usually at presentation or developing shortly after if proteinuria persists at >3.5 g/24 h.

c Provided patients are not receiving immunosuppressive therapy previously or at the time of renal biopsy.

Renal survival by response to immunosuppressive agents in children with SRNS (*PoDoNet cohort)

*Trautmann et al. JASN. 28: 3055-3065, 2017

KDIGO Controversies Conference on Glomerular Diseases
November 16-19, 2017 | Singapore
Problems with treatment studies in FSGS/SRNS*

• Heterogeneous population
  – Recruitment of patients with adaptive FSGS, including patients with proteinuria without nephrotic syndrome
  – No requirement for EM in studies so the extent of foot process effacement not known
  – Inclusion of patients with FH of nephrotic syndrome; lack of genetic studies
  – Inclusion of patients with primary and delayed steroid resistance
  – Inclusion of patients with MCD and MesPGN

• Inadequate patient recruitment so the studies are underpowered to detect a difference between treatment groups

# Interventions for SRNS (FSGS/MCD): RCTs

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration (mths)</th>
<th>Remission (Complete + Partial)</th>
<th>RR (95% CI) for remission</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS-CT 2011</td>
<td>138 A+C</td>
<td>Cyclosporin</td>
<td>MMF + dexamethasone</td>
<td>12</td>
<td>33 (46%) vs 22 (33%)</td>
<td>1.35 (0.90-2.10)</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Ren 2013</td>
<td>33 A</td>
<td>Tacrolimus + prednisone</td>
<td>IV CPA + prednisone</td>
<td>6</td>
<td>10 (67%) vs 10 (56%)</td>
<td>1.20 (0.69-2.07)</td>
<td>No significant difference</td>
</tr>
<tr>
<td>APN 2008</td>
<td>32 C</td>
<td>Cyclosporin + prednisone</td>
<td>IV CPA + prednisone</td>
<td>3</td>
<td>9 (60%) vs 3 (18%)</td>
<td>3.40 (1.12-10.28)</td>
<td>Remission CSA &gt; CPA</td>
</tr>
<tr>
<td>Gulati 2012</td>
<td>124 C</td>
<td>Tacrolimus + prednisone</td>
<td>IV CPA + prednisone</td>
<td>12/6</td>
<td>53 (80%) vs 28 (43%)</td>
<td>1.80 (1.34-2.42)</td>
<td>Remission Tac &gt; CPA</td>
</tr>
<tr>
<td>Magnasco 2012</td>
<td>31 C</td>
<td>Rituximab/ Cyclosporin/ prednisone</td>
<td>Cyclosporin/ prednisone</td>
<td>3</td>
<td>3 (19%) vs 3 (20%)</td>
<td>0.94 (0.22-3.94)</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Sinha 2017</td>
<td>60 C</td>
<td>Tacrolimus + prednisone</td>
<td>MMF + prednisone</td>
<td>12</td>
<td>28 (90%) vs 13 (45%)</td>
<td>2.01 (1.32-3.07)</td>
<td>Maintains Remission Tac &gt; MMF</td>
</tr>
</tbody>
</table>
Other immunosuppressive treatments for FSGS

• mTOR inhibitors
  – Evidence that mTOR inhibitors can exacerbate FSGS

• ACTH gel (Hogan. CJASN 8: 2072-2081, 2013; NCT01155141; NCT01129284)
  – Report of 24 patients with FSGS (6 steroid dependent; 15 steroid resistant) treated with ACTH gel (80 units twice weekly sc for variable duration).
  – 7 showed response (CR 2, PR 5) including 5 with SRNS; 5 had sustained response (range 23-104 weeks) and 2 relapsed
  – 21 had adverse effects; 23 episodes of corticosteroid-like adverse effects

• ACTH gel in children
  – NCT02972346: RCT in China comparing ACTH gel with no specific treatment in ages 3-12 years for SDNS/SRNS
  – NCT02132195: RCT in USA comparing ACTH gel with no specific treatment in ages 2-20 years for FRNS/SDNS with FSGS or MCD; SRNS excluded
Investigational treatments for primary FSGS*

• Blocking TGF-β reduces fibrosis in experimental CKD
  – Fresolimumab (monoclonal antibody against 3 isoforms of TGF-β)
    • Phase 1 study: 3/16 had ≥ 50% reduction in proteinuria
    • Phase 2 study: 2/36 achieved PR. (Vincenti et al Kid Int Rep (2017) 2: 800-810; NCT01665391)

• TNF-α can mediate proteinuria and fibrosis in FSGS
  – Adalimumab is a monoclonal antibody against TNF-α
    • FONT Study (1): 4/10 had 50% reduction in proteinuria
    • FONT Study (2): 0/7 had any reduction in proteinuria

• Blocking B7-1 (CD80) expression with abatacept
  – Remission in 4 patients with rFSGS & 1 with primary FSGS; all had B7-1 staining of podocytes (Yu 2013)
  – Response in 1 of 25 other reported patients with rFSGS
  – Crossover RCT comparing abatacept with placebo in 90 patients (adults/children with MCD or FSGS; not post Tx recurrence) commenced in 2016; results in 2020 (NCT02592798)

*Trachtman 2017: Expert Opinion on Investigational Drugs 2017; 26: 945-952
Investigational treatments for primary FSGS*

- Angiotensin type 1 & endothelin receptors type A promote vasoconstriction & extracellular matrix accumulation
  - DUET study: RCT comparing sparsantin with irbesartan for 8 weeks in 96 patients with FSGS (Trachtman ASN abstracts 2016, 2017: NCT 01613118)
  - UPC <1.5 g/g in 28% SPAR vs 9% IRB
  - Benefit persisted for 48 weeks in extension study
- Binding of circulating factors
  - Galactose can bind circulating factors
  - 0/7 children on galactose achieved CR or PR (Sqambat 2013; NCT01113385)
  - 2/7 treated with Galactose and 2/7 treated with standard therapy achieved PR (FONT 2, 2015: NCT00814255)

*Trachtman 2017: Expert Opinion on Investigational Drugs 2017; 26: 945-952
Other investigational treatments for FSGS*

- **Blocking JAK/STAT pathway**
  - Rationale: JAK/STAT inhibitor reverses increased glomerular permeability to albumin after exposure to FSGS plasma or cardiotrophin-like cytokine factor-1 (CLCF-1)

- **Retinoic acid treatment (NCT00098020)**
  - Rationale: Retinoids restore podocyte phenotype and reduces proteinuria
  - Phase 1 study of isotretinoin in 10 adults with MCD/FSGS for 6 months completed

- **Blocking Notch 1**
  - Rationale: Significant activation of Notch 1 in FSGS
  - Signature of this pathway in FSGS patients could identify patients for trials of Notch 1 inhibitors

- **Complement antagonists**
  - Rationale: 5 of 19 patients in FSGS-CT showed complement activation
  - Demonstrating complement activation could allow eculizumab use in a subset of FSGS patients

- **Infusion of mesenchymal stem cells**
  - Rationale: Improvement in experimental models of kidney disease
  - NCT02382874 currently recruiting

*Trachtman 2017: Expert Opinion on Investigational Drugs 2017; 26: 945-952
“Neptune” schema for integrative genomics of nephrotic syndrome*

Remember the child/adult/family with nephrotic syndrome*

- Understandable
- Individualized
- Accurate
- Credible
- Timely

Getting the Right Information

- Tracking/Monitoring
- Knowing what to look for
- Preventing & managing relapse
- Managing medications & side effects
- Diet

Understanding the Diagnosis & Approach to Treatment

- Getting a diagnosis
- Understanding NS
- Knowing what to expect
- Learning about medications

Learning to Manage NS

*Beanlands NDT (2017) 32: i98 - i105
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