Treatment of Focal Segmental Glomerulosclerosis

Hong Kong 2015.12.13

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- First described in 1957 by Rich
- Accounting for 10% ~ 30% of all renal biopsies
- Incidence has been increasing recently
- Typical manifestations:
  - Obvious proteinuria
  - Hypertension
  - Worsening renal insufficiency
- One of the common causes of ESRD

Nephrol Dial Transplant 2009, 24: 870–876
The Epidemiology of FSGS (Global)

- **America:**
  - Adults NS—40%; Children NS—20%
  - Incidence of FSGS-ESRD: 7 pmp
  - Renal biopsies:
    - 12.2% (Haas M, 1995)-18.7% (D’Agati, 1994)

- **South Korea:**
  - Renal biopsies: 5.9% (1997-2001)
The Epidemiology of FSGS (China)

- **China:**
  - Peking University First Hospital: 3.3%(1998-2002), 3.8%(2003-2007)
  - Ruijin Hospital: 16.7%(2003-2005), 18.5%(2006-2008)

Pathological Feature

**LM:** Focal Segmental Glomerulosclerosis

**EM:** foot-process effacement

**IF:** deposits of IgM and C3
Pathologic Classification

Fogo, A. B. *Nat. Rev. Nephrol*; doi:10.1038/nrneph.2014.216
Characteristics & Outcomes

- Most common
- Tubulointerstitial lesion
- Massive proteinuria

- Also in secondary FSGS, DM, obesity etc.

- Best prognosis
- Steroid-sensitive NS

- Accidental onset
- Poorest prognosis
- Frequent in African Americans
- Poor response to steroid

Etiology Classification

Primary FSGS
- Unknown

Secondary FSGS
- Obesity, reflux nephropathy, drugs, infections, ...

Familial FSGS
- Mutations of podocyte related molecules

References:
- Ren Fail. 2003; 25: 759-764
- Kidney Int. 1996; 50: 1582-1590
- Nat Med. 2011; 17: 952-960
- Pediatr Nephrol. 2004; 19: 1075-1092
Pathogenesis mechanism

- **Permeability factors**
  - Circulating factor
    - suPAR
    - IL-13
  - Podocyte-associated molecules
    - Angptl4
    - Integrinβ 3

- **toxicity**
  - Viral infection, drugs, heavy metal, etc.
  - Collapsing is common

- **hemodynamics**
  - Decreased nephron mass
  - Low birth weight
  - Vessel dilation
  - Hillar type is common

- **heredity**
  - Podocyte genes mutations
  - Other genes mutations

Reviewed in Parikh, AJKD 59: 336, 2012
Familial FSGS

genetic mechanism
Pathogentic genes of FSGS

Membrane ionic channel
- **TRPC6** (adults)

Slit Diaphragm
- **NPHS1** (children)
- **NPHS2** (children, adults)
- **CD2AP** (children)

Cytoskeleton
- **ACTN4** (adults)
- **INF2** (adults)

Transcription Factors
- **WT1** (children)
- **PAX2** (children)
- **Lmx1b** (children)

References:
- Kestila M. Molecular Cell. 1998(1):575-582
- Putaala H. Hum Mol Genet 10:1-8
- Nat Genet. 2000 Apr;24(4):349-54
- Science. 2005 Jun 17;308(5729):1801-4
- Nat Genet. 2000 Mar;24(3):251-6
- **Location:** 14q32
- **Encoding forming nucleation factor — actin-regulating proteins**
- **Mutations cause adult-onset FSGS (2010)**
- **Mutation rate:** 9.8%–17% (most common in Caucasian)
- **Pathogenic mutations mainly locate in DID domain**

**Diagram: Podocyte cytoskeleton protein — INF2**

- **DID**
- **FH1**
- **FH2**
- **DAD/WH2**

**Exon 2:**
- A13T, L42P,
- L57P, L76P,
- C104R, C104W,
- R106P, L128P

**Exon 3:**
- L132R,
- A164_D166del,
- L165P

**Exon 4:**
- R177H, E184K,
- E184Q, S186P,
- Y193H, L198R,
- N202D, A203D,
- R214C, R214H,
- R218Q, R218W, E220K

**References:**
- *Proc Natl Acad Sci U S A.* 2011 Feb 15;108(7):2933-8
Novel mutations in the *inverted formin* 2 gene of Chinese families contribute to focal segmental glomerulosclerosis

Jingyuan Xie¹,⁶, Xu Hao¹,⁶, Evren U. Azeloglu², Hong Ren¹, Zhaohui Wang¹, Jun Ma¹, Jian Liu¹, Xiaodan Ma³, Weiming Wang¹, Xiaoxia Pan¹, Wen Zhang¹, Fang Zhong¹, Yifu Li⁴, Guoyu Meng³, Krzysztof Kiryluk³, John Ciiian He⁵, Ali G. Gharavi⁴ and Nan Chen¹

- **Autosomal Dominant**
- 55 adult-onset FSGS families, 34 IgAN families
- The largest pedigree including 100 family members, 11 affected individuals
- Onset age: 20~60, massive proteinuria and ESRD
14q32 LOD: 3.52

*p.S85W* abolishes the hydrogen bonding network in the inner core of the protein

Xie J, Hao X, …., Chen N. Kidney international 2015
*p*.S85W affects the cytoskeleton

- Mutation rate in our study is 3.6%.
- *p*.S85W mutation affects the interaction between INF2 and Cdc42, which may lead to decreased activation of SRF, leading to abnormal cytoskeletal and morphological changes of podocyte.
- The mechanism of *p*.S129_Q130insVRQLS mutation is still unknown.

Xie J, Hao X, ...., Chen N. Kidney International 2015
Family FSGS research 2
—gene sequencing

Article

**COL4A3** mutations cause focal segmental
glomerulosclerosis

Jingyuan Xie¹,*, Xiaoxi Wu²,*, Hong Ren¹, Weiming Wang¹, Zhaohui Wang¹, Xiaoxia Pan¹, Xu Hao¹, Jun Tong¹, Jun Ma¹, Zhibin Ye³, Guoyu Meng⁴, Yufei Zhu⁵, Krzysztof Kiryluk⁵, Xiangyin Kong², Landian Hu²,*, and Nan Chen¹,*

- 40 FFSGS families
- 50 sporadic FSGS
- **Methods:** exome sequencing and sanger sequencing
- Exclude patients with **ACTN4, TRPC6** or **INF2**

mutations
**COL4A3 mutations cause FFSGS**

- 5/40 (12.5%) family with *COL4A3* heterozygous mutation
- 1/50 sporadic patients with *COL4A3* heterozygous mutation

Xie J, Wu X, Ren H, Wang W, ..., Chen N. JMCB
All six variants were located in a highly conserved region of **COL4A3**

**Structural predictions:** The *p. Cys1616Tyr* variant disrupts the Cys-Cys bond, the interior core, and the overall fold of the protein.

**COL4A3 mutations cause FFSGS**

*Xie J, Wu X, Ren H, Wang W, …, Chen N. JMCB*
**Study design:**

- 81 adults from 76 families;
- 24 families had a history of renal diseases
- **Target NGS panel:** covering 39 genes

**Results:**

- Confirmed pathogenic mutations: 10/81 (12%)
- Probably pathogenic mutations: 6
- Total mutation rate: 16/81 (20%)
  - Familial 22%, sporadic 10%
  - **COL4A3-5 mutation:** 8/81 (9.8%)
Hereditary COL4A3/COL4A4 variants mistaken for FFSGS?

DUKE study: COL4A3 mutation rate in FFSGS is 10%

- Mutations in COL4A3 and COL4A4 are known to cause AS, TBMN
- Secondary FSGS is known to develop in classic AS at later stages
- In all 7 families, there were individuals with histologic features of FSGS by LM.
- In one family, EM showed thin GBM. other families had variable findings inconsistent with classical AS.

Redefining the spectrum of the disease?

- A subset of renal manifestations associated with \textit{COL4A3} or \textit{COL4A4} variants cannot be distinguished from FSGS by clinical data or histopathology

- Redefining the spectrum of Alport syndrome?

## Mutation rate of known genes in FSGS

<table>
<thead>
<tr>
<th>category</th>
<th>Number</th>
<th>Mutation rate</th>
<th>Reported rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPHS2 SRNS</td>
<td>44</td>
<td>0 (0)</td>
<td>0-18% (children)</td>
</tr>
<tr>
<td>FSGS</td>
<td>77</td>
<td>1 (1.3%)</td>
<td>4-24%</td>
</tr>
<tr>
<td>ACTN4 FSGS</td>
<td>80</td>
<td>1 (1.25%)</td>
<td>3.5%</td>
</tr>
<tr>
<td>TRPC6 FSGS</td>
<td>80</td>
<td>2 (2.5%)</td>
<td>2.3~20%</td>
</tr>
<tr>
<td>INF2 FSGS</td>
<td>55</td>
<td>2 (3.6%)</td>
<td>16%</td>
</tr>
<tr>
<td>COL4A3 FSGS</td>
<td>40</td>
<td>5 (12.5%)</td>
<td>10%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>21.2%</td>
<td>35-80%</td>
</tr>
</tbody>
</table>

In over 70% pedigrees, no mutation is detected, indicating that lots of potential pathogenic genes need to be investigated.

Zhu B et al, Mutation Res 2009  
Zhang Q et al, Contr Nephrol 2013  
Overview

Pathogenesis

Diagnosis and Treatment
• **Patients:**
  - 2005~2012, 124 FFSGS patients (83 families)
  - 124 primary FSGS patients

• **Diagnostic criteria of FFSGS:**
  - More than one family member are biopsy-proven FSGS
  - One has biopsy-proven FSGS, other have proteinuria, progressive renal dysfunction or ESRD
  - AS, FD, TBMN or other hereditary kidney diseases were excluded
• **Basic information**
  - Gender, age, blood pressure, first episode, disease course

• **Laboratory examination**
  - Blood/urine routine, 24H urine protein, renal function
  - eGFR was calculated by MDRD

• **Outcome**
  - ESRD
  - Remission of proteinuria (at least 50% decline)
## Baseline characteristics

**Table 1.** Clinicopathological characteristics of FFSGS and SFSGS

<table>
<thead>
<tr>
<th></th>
<th>FFSGS</th>
<th>SFSGS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>124</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>71/53</td>
<td>76/48</td>
<td>0.096</td>
</tr>
<tr>
<td>Follow-up months</td>
<td>28.3±12.5</td>
<td>26.5±19.5</td>
<td>0.081</td>
</tr>
<tr>
<td>Age of onset</td>
<td>34 (10–62)</td>
<td>40 (12–80)</td>
<td>0.035</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>43.75</td>
<td>35.16</td>
<td>0.079</td>
</tr>
<tr>
<td>Serum creatinine, μmol/l</td>
<td>174.3±186.6</td>
<td>153.0±144.2</td>
<td>0.086</td>
</tr>
<tr>
<td>Uric acid</td>
<td>415.6±118.1</td>
<td>397.9±109.4</td>
<td>0.275</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>69.49±38.27</td>
<td>81.76±50.47</td>
<td>0.069</td>
</tr>
<tr>
<td>Hematuria, %</td>
<td>62.9</td>
<td>22.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Proteinuria, g/day</td>
<td>1.1 (0.03–5.6)</td>
<td>1.5 (0.05–8.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Nephrotic syndrome, %</td>
<td>13.3</td>
<td>22.6</td>
<td>0.029</td>
</tr>
<tr>
<td>Focal glomerulosclerosis, %</td>
<td>13.23±11.83</td>
<td>15.71±13.49</td>
<td>0.141</td>
</tr>
<tr>
<td>Global glomerulosclerosis, %</td>
<td>25.56±21.4</td>
<td>16.52±20.96</td>
<td>0.0007</td>
</tr>
<tr>
<td>Tubulointerstitial lesion score</td>
<td>4.07±0.28</td>
<td>3.00±0.1</td>
<td>0.0004</td>
</tr>
<tr>
<td>Remission of proteinuria, %</td>
<td>23.08</td>
<td>48.39</td>
<td>0.042</td>
</tr>
<tr>
<td>End-stage renal disease, %</td>
<td>27.42</td>
<td>2.42</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Remission of proteinuria was defined as a proteinuria decline of at least 50% of the baseline level. Hematuria was defined as more than 3 red blood cells in each high-power field.

## Renal Outcome

<table>
<thead>
<tr>
<th></th>
<th>FFSGS</th>
<th>SFSGS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR/CR</td>
<td>23.08%</td>
<td>48.39%</td>
<td>0.042</td>
</tr>
<tr>
<td>ESRD</td>
<td>27.42%</td>
<td>2.42%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Comparison between FFSGS and SFSGS

**FFSGS**
- More hematuria
- Lower proteinuria
- Less NS
- More severe pathological lesions
- Less CR/PR
- More ESRD

**SFSGS**
- Higher proteinuria
- More NS
- Less severe pathological lesions
- More CR/PR

Initial treatment

- Steroid and immunosuppressive therapy be considered only in idiopathic FSGS associated with NS. (1C)

- Prednisone: a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg). (2C)
Initial treatment

- Initial high dose of steroids is given for a minimum of 4 weeks, up to a maximum of 16 weeks until complete remission (2D)

- Steroids be tapered slowly over a period of 6 months after achieving complete remission (2D)

- CNIs: first-line therapy —— patients with contraindications or intolerance to high-dose steroids (2D)
Relapse treatment

- Same to MCD

- CTX 2-2.5mg/kg/d, po. 8wks (2C)

- For Recurrence patients after CTX treatment, CsA 3-5mg/kg/d or FK506 0.05-0.1mg/kg/d, po (2C)
Question 1——
Corticosteroid benefit for moderate proteinuria?

Design（RCT study）

- **Participants**: primary FSGS patients with moderate proteinuria
- **ACEI/ARB group**(n=30), corticosteroid group(n=30)
- **Follow-up**: 12 months
- **Results**: higher rate of proteinuria remission in corticosteroid group compared to ACEI/ARB group

<table>
<thead>
<tr>
<th>proteinuria (g/24h)</th>
<th>group</th>
<th>0 m</th>
<th>6 m</th>
<th>p value</th>
<th>12 m</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>1.96±0.16 g</td>
<td>1.67±0.33</td>
<td></td>
<td>0.432</td>
<td>1.71±0.44</td>
<td>0.596</td>
</tr>
<tr>
<td>corticosteroid</td>
<td>1.75±0.19 g</td>
<td>0.69±0.16</td>
<td>&lt;0.001</td>
<td>0.48±0.12</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Steroid treatment: 8 vs 12wks

<table>
<thead>
<tr>
<th>Duration</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
<th>Effective rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 wks</td>
<td>30</td>
<td>15</td>
<td>18</td>
<td>70.31</td>
</tr>
<tr>
<td>12 wks</td>
<td>30</td>
<td>16</td>
<td>15</td>
<td>71.87</td>
</tr>
</tbody>
</table>

P > 0.05

Extending steroid treatment to 12 wks resulted in a similar remission rate but more side-effects

Nan Chen, WCN 2013: SU151
Question 2——
Extend duration of initial steroid treatment?

Extending treatment to 10wks resulted in a same remission rate

Advent events in week 10

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>elevated AST/ALT</td>
<td>29</td>
</tr>
<tr>
<td>Infection</td>
<td>16.1</td>
</tr>
<tr>
<td>cushing syndrome</td>
<td>16.1</td>
</tr>
<tr>
<td>steroid diabetes</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Zhang J, Liu ZH et al. CNDT, 2008 -18（1），13-19
**Question 3:** Immunosuppressive Agents——CTX?

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>steroid-sensitive+CTX</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>steroid-resistant+CTX</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**CTX can be used as a second-line therapy?**

**Response to FK506**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total remission</td>
<td>23 (52.2%)</td>
</tr>
<tr>
<td>CR</td>
<td>17 (38.6%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>6 (13.6%)</td>
</tr>
<tr>
<td>Time to remit (weeks)</td>
<td>15.28 ± 6 (04–24)</td>
</tr>
<tr>
<td>FSGS variants</td>
<td>TAC responsive</td>
</tr>
<tr>
<td>FSGS-NOS (n = 33)</td>
<td>18 (54.5%)</td>
</tr>
<tr>
<td>Cellular variant (n = 08)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Tip variant (n = 03)</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>Relapse during tapering</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Relapse after completion of therapy</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Complications</td>
<td>29 (65.9%)</td>
</tr>
</tbody>
</table>

SR-FSGS, steroid-resistant focal segmental glomerular sclerosis; NOS, not otherwise specified; TAC, tacrolimus.
**Participants**: steroid-dependent or steroid-resistant FSGS

- **CTX group** N=18, **FK506 group** N=15
- **Follow-up**: 12 months

**Result**: CTX and TAC had a similar efficacy

---

**Table 3.** Comparison of remission rate between CTX and FK-506 groups, n (%)

<table>
<thead>
<tr>
<th>Duration</th>
<th>CTX NR</th>
<th>remission</th>
<th>FK-506 NR</th>
<th>remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR (44.4%)</td>
<td>10 (55.6%)</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PR (38.9%)</td>
<td>7 (16.7%)</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>6 months</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>6</td>
<td>9 (50.0%)</td>
<td>3 (16.7%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 (66.7%)</td>
<td></td>
<td>11 (73.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PR (50.0%)</td>
<td></td>
<td>5 (33.3%)</td>
</tr>
</tbody>
</table>

**P**

- 0.77
- 0.97

**CTX is preferable for its price**

Hong Ren ... Nan Chen. Am J Nephrol, 2013, 37: 84-90
## Immunosuppressive Agents

**CTX vs FK-506**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>CTX (n = 18)</th>
<th>FK-506 (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections*</td>
<td>9 (50.0%)</td>
<td>2 (13.3%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated glucose*</td>
<td>0</td>
<td>4 (26.7%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Elevated transaminase</td>
<td>1 (5.6%)</td>
<td>1 (6.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Deterioration of renal function</td>
<td>1 (5.6%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Menstruation disorders</td>
<td>1 (5.6%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2 (11.1%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1 (5.6%)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS = Non-significant difference; URTI = upper respiratory tract infection; UTI = urinary tract infection. *p < 0.05 indicates a significant difference between CTX and FK-506 groups.*

Hong Ren ... Nan Chen. Am J Nephrol, 2013, 37: 84-90
Multicenter, RCT

Participants: steroid-resistant FSGS, N=138
   (MMF group N= 66, CsA group N= 72)

Dose: CsA 4.6±1.7 mg/kg/d
   MMF 26.2±6.1 mg/kg/d

Result:
   • Same PR and CR rate at 12 month (MMF 33% VS CsA 46%)
   • Same remission rate for extra 26 weeks.
**Question 4- Rituximab**

- Single center, prospective
- FSGS-NS patients, N=18
  (Steroid-dependent/resistant, CNI/MMF-resistant)

**Treatment:** Rituximab

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>8m later</th>
<th>12m later</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS</td>
<td>PR</td>
<td>NR</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8</td>
<td>17</td>
</tr>
</tbody>
</table>

• Multi-center, prospective

• N=30
  ✓ Children (N=10)
  ✓ Adult (N=20)
  ✓ MCD/MesGN (N=22)
  ✓ FSGS (N=8)

• SDNS OR FRNS

• 1-2 doses of RTX (375mg/m²)

• Follow-up: 1 yr

• Result:
  ✓ 100% remission
  ✓ 60% treatment-free
  ✓ 50% never relapsed
Patients: FSGS-NS, N=12 (SDNS, SRNS), no response to CTX, MMF, CsA/Tac, average duration 2-10 years

Treatment:
- 375mg/m²/w, 2-4 times
- Tapering steroid and immunosuppressive agents within 3-6 months
- Reapply Rituximab when CD19 count >1% or >15/ul

Follow-up: 6-18 month

Efficacy: All achieved CR, no relapse

Ruijin Hospital unpublished data
一般情况：男，17岁，学生

病史简介：

5年前无明显诱因下出现颜面、双下肢浮肿伴泡沫尿，2010年10月、2011年6月二次外院肾穿病理提示FSGS（NOS型），期间予“激素＋干细胞”（2010.10-11.6）、“激素＋环孢素”（2011.6-2012/2）、“激素＋FK506”（2012.2-2012.8）、“激素＋FK506+MMF”（2012.8-2012.9）治疗，治疗过程中NS一度缓解，但反复复发。2年前我院就诊，当时24蛋白定量16398-25889mg/24h，Alb19g/l，Scr41umol/l，调整治疗方案为“激素＋FK506＋CTX”（2012.9-2014.10）治疗，规范治疗15月后NS完全缓解，4月后因上感后NS再次复发。

查体：BP：115/62mmHg，神清、满月脸、双肺呼吸音偏低，心率80次/分，腹软，腹部皮肤紫纹明显，双下肢浮肿。
治疗经过

• 2014.10考虑NS复发，在“激素40mg / d＋FK506 4mg / d”基础上加用美罗华 375mg/m2治疗。

• 2次疗程后（2014.10.27、2014.11.3），NS完全缓解，予激素减至25mg / d。

• 2014.12、2015.2再次分别予美罗华治疗，治疗期间病情稳定，激素、FK506逐渐减药。

• RTX治疗期间无药物相关性不良反应。

• 随访期间无复发及不良反应反应。
24h proteinuria and albumin before and after treatment

Alb (g/l)  24h proteinuria(g/24h)

- Prednison + Stem cell
- Prednison + Cyclosporin
- Prednison + Fk506
- Prednison + Fk506 + MMF
- Prednison + Fk506 + CTX

Ruijin Hospital unpublished data
## B cell counts during the treatment

<table>
<thead>
<tr>
<th>RTX Treatment</th>
<th>Durition (month)</th>
<th>Lymphocyte (10⁹/l)</th>
<th>CD19+ (%)</th>
<th>CD20+ (%)</th>
<th>CD19+ (个 / ul)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/4</td>
<td>4</td>
<td>4.2</td>
<td>4.4</td>
<td>168</td>
</tr>
<tr>
<td>RTX (375mg/m²) + Perdnision (40mg)+ FK506(4mg/d)</td>
<td>1</td>
<td>3.6</td>
<td>0.3</td>
<td>0.5</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.5</td>
<td>0.1</td>
<td>0.5</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4.1</td>
<td>0.1</td>
<td>0.1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4.1</td>
<td>0.1</td>
<td>0.1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>4.1</td>
<td>0.1</td>
<td>0.1</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*Ruijin Hospital unpublished data*
Summary

- Exact pathogenic genes only account for small part of FSGS

- Next-gen sequencing helps to explore novel genes

- Mutation rate of INF2 in Chinese familial FSGS is 3.6%

- COL4A3 mutations account for 12.5% of AD FSGS

- Reclassification of Alport syndrom is suggested, “Collagen IV related nephropathy”?
Heterogeneous clinical manifestations of FSGS

- FFSGS less response to treatment and a worse renal prognosis

Treatment:

- Lack of high-quality RCT study especially in Chinese patients
- Steroid therapy could be considered for moderate proteinuria
- Extend steroid treatment may not be suggested
- Rituximab is promising but need more data
Acknowledgement

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• All members in 973 Program

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