Treatment of Steroid-Resistant Nephrotic Syndrome (SRNS) in Children

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Steroid Sensitive Nephrotic Syndrome

Like an excited movie!- Part 1
1937-Discovered "Nobel Prize-1950" (E.Kendall/Wintersteiner, T. Reichstein, Ph. S. Hench)
Expectations from the treatment options

Summary - Part 1
Result!

Summary - Part 1
Steroid-Resistant Nephrotic Syndrome (SRNS)

The movie starts!! - Part 2
Outline

• Definition of steroid resistance
• KDIGO- The agents used in the treatment of SRNS
  - Calcineurin inhibitors (CNIs)
  - RAS blockade
  - Mycophenolate mofetil (MMF)
  - High-dose steroids
  - Alkylating agents
  - Recent advances in treatments of SRNS/FSGS
• Conclusion
Steroid Resistance - Definition

- Idiopathic NS (< 16 years) - 1-3/100000
- 20% steroid resistant
- Minimal-change disease (MCD), Mesangial proliferative glomerulonephritis (MesPGN), or Focal segmental glomerulosclerosis (FSGS), etc

Steroid Resistance
Failure to achieve complete remission after initial therapy with corticosteroids

The PodoNet Registry Cohort

67 centers in 21 countries, 1655 patients with NS through an online portal

SRNS manifested in the first 5 years of life 64%

The most common histopathologic diagnoses; FSGS (56%), MCD (21%), and MesPGN (12%)

A genetic disease cause was identified in 23.6%; NPHS2 (n=138), WT1 (n=48), and NPHS1 (n=41) were most common

KDIGO-Definition of steroid resistance

- **Minimum of 8 weeks treatment with steroids (2D)**
- A diagnostic kidney biopsy
- Evaluation of kidney function by glomerular filtration rate (GFR) or estimated GFR (eGFR)
- Quantitation of urine protein excretion

If partial or complete remission is not achieved, 50% risk of progression to ESKD within 5 years of diagnosis

Steroid dose, duration?

**ISKDC**

- 60 mg/m²/d - 8 weeks
- 4 weeks 2 mg/kg/d + 4 weeks 40 mg/m² (or 1.5 mg/kg)/alternate days

Remission is still possible after 8 weeks?

ISKDC. Lancet. 1974
Kidney Biopsy

- Determine the underlying pathology (may dictate therapy)
  (for FSGS; > 20 glomeruli)
- Information on the degree of interstitial and glomerular fibrosis (prognosis)

GFR or eGFR

- A predictor of the long-term risk for kidney failure

Quantitation of urine protein excretion

- Urinary protein/creatinine ratio on the first morning specimen or measurements of 24-h urine protein may be used.
- Should be evaluated at diagnosis and during treatment
- Helps to determine treatment response (partial, complete, or no remission)
Calcineurin Inhibitors (CNIs)-KDIGO

Using a CNI as initial therapy for children with SRNS is recommended (1B)

CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved (2C)

It has been suggested to continue for a minimum of 12 mo, if at least a partial remission is achieved by 6 months (2C)

KDIGO suggest that low-dose corticosteroid therapy be combined with CNI therapy (2D)

62% used CNI as first-choice second-line in PodoNet

Lombel RM ve ark. Pediatr Nephrol 2013
## Randomized controlled trials in SRNS

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<th>Author</th>
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<th>Remission (complete/partial)</th>
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<tr>
<td>Lieberman &amp; Tejani 1996</td>
<td>24</td>
<td>CyA</td>
<td>Placebo</td>
<td>6</td>
<td>%100-%17</td>
<td>CyA &gt; placebo</td>
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<td>Ponticelli C, et al. 1993</td>
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<td>CyA</td>
<td>Supportive therapy</td>
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<td>%60-%0</td>
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<td>Garin EH, et al. 1998</td>
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<td>CyA</td>
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<td>2</td>
<td>%0-%0</td>
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<td>Choudhry S, et al. 2009</td>
<td>41</td>
<td>TAC+Pred*</td>
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<td>138</td>
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<td>3</td>
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**CPA; cyclophosphamide, CyA; Cyclosporine, MMF; mycophenolate mofetil, *alternate days, **6 months full dose followed by taper 25% every 2 months**
PodoNET-Medication protocols applied in 1234 patients

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CNIs-Problems/Questions

The optimal duration of treatment with CNIs?
* Reduction in proteinuria; 4.4 ± 1.8 wk
** The average time for complete/partial remission; 8-12 wk

Relapse rate 70% within 6-12 months after the discontinuation of treatment

Mostly used longer than 12 months to reduce relapse, long-term effects? (risk of relapse, renal function, nephrotoxicity, etc.)

The most effective blood level?

**Choudhry S et al. Am J Kidney Dis 2009
Renin-angiotensin system (RAS) blockade for SRNS-KDIGO

**KDIGO recommends treatment with angiotensin converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) for children with SRNS (1B)**

Significant reduction in proteinuria with enalapril* and fosinopril **

* 0.2 mg / kg / dose causes 33% reduction in proteinuria
* 0.6 mg / kg / dose causes 52% reduction in proteinuria

*eGFR and K monitoring are important*

*Bagga A et al. Pediatr Nephrol 2004
**Yi Z et al. Pediatr Nephrol 2006*
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Therapies for children failing to respond to CNIs-KDIGO:

Mycophenolate mofetil (MMF) (2D), high-dose corticosteroids (2D), or a combination of these agents (2D) be considered in children failing to achieve complete or partial remission with CNIs and corticosteroids.
138 (93 children), Primary SRNS and FSGS

**MMF**

- MMF + high-dose dexamethasone
- Cyclosporine

**Complete or partial remission**

- %33
- No significant difference
- %46

_Gipson DS et al. Kidney Int 2011_
** Observational studies, 42 children, minimum treatment period with MMF; 6 months

- Complete remission rate: %23-62
- Partial remission rate: %25-37
- No remission: %8-40

Li Z et al. Pediatr Nephrol 2010
de Mello Vr et al. Pediatr Nephrol 2010
128 children, 67 SRNS (65 FSGS), retrospective study

6mo-21 years follow up

MMF

TAC

CsA

RTX

MMF+TAC+pred

Complete/partial remission rates

67%

77%

54%

25%

67%

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High-Dose Corticosteroids

78 children with SRNS, a comparator study

6 alternate-day pulses of methylprednisolone (30 mg/kg) or dexamethasone (5 mg/kg) iv + prednisone orally

Short-term outcome at the end of a 2-week regimen

Methylprednisolone
- 33.3% complete remission
- 14.3% partial remission

Dexamethasone
- 35.1% complete remission
- 12.3% partial remission

Hari P et al. Indian Pediatr 2004
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RCTs/Observational Studies;

- With the extended duration of steroid treatment, complete or partial remission rate: 33% - 53%, respectively
- Complete and partial remission rates in 138 patients were similar both in CsA and MMF + dexamethasone group!
- In contrast, RCTs in which the control arm received no corticosteroids, 0 - 17% achieved remission!!
- *A retrospective study (52 patients): remission rate was higher in patients receiving CsA + methylprednisolone than the patients taking CsA + oral prednisone

ISKDC. Lancet. 1974
Gipson DS et al. Kidney Int 2011

Ponticelli C et al. Kidney Int 1993
*Ehrich JH et al. NDT 2007
Alkylation agents

2 RCTs, 84 children with SRNS

Cyclophosphamide + prednisone therapy was not superior to prednisone

KDIGO - Cyclophosphamide should not be used in children with SRNS

ISKDC, Lancet, 1974
Latta K et al. Pediatr Nephrol 2001
Hodson EM et al. Cochrane Database 2010
KDIGO-2012
Rituximab- anti-CD20 monoclonal Ab

375 mg/m² weekly or biweekly

Treg regulation

Podocytes stabilization in FSGS

Effective in SSNS
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**59.1%**
A questionnaire filled by members of the IPNA;

SDNS/FRNS N=28
82%

SRNS N=27
44%

Post-transplant recurrence of NS N=15
?? 60%-accompanying treatments!

Good initial response, 27% acute reactions

Prytuła A et al. Pediatr Nephrol 2010
Rituximab - Problems/Questions

- The lack of RCTs, different results?, doses?
- The risk for serious adverse events, which may persist long after treatment discontinuation
- Long-term effect? - There is a developing immune system in children, effectivity of vaccines !?
- **Cost** (1 RTX dose: ~441 £ vs CsA 1 year: 900 £, TAC 1 year: 3400 £)
- *It is not as effective in SRNS as in SSNS (observational studies)*
- Rituximab dependency?
- Anti-rituximab autoantibodies may be a concern after repetitive infusion of RTX

Prytula A et al. Pediatr Nephrol 2010
Ahn YH et al. Pediatr Nephrol 2014*
No significant differences between:

- TAC vs CsA (1 study, 41 children)
- CsA vs MMF+ IV dexametazone (1 study, 138 children)
- Oral CPH + prednisone vs prednisone alone (2 studies, 91 children)
- IV CPH vs oral CPH (1 study, 11 children)
- IV CPH vs oral CPH+ IV dexametazone (1 study, 49 children)
- AZT+ prednisone vs prednisone alone (1 study, 31 children)
- TAC+CPH+Pre vs TAC+MMF+Pre vs TAC+leflunomide+Pre (1 study, n:18)
- RTX+CsA+Pre vs CsA+Pre (1 study, 31 children)

CNIs increase the likelihood of complete/partial remission compared with placebo/no treatment or CPH

Hodson EM et al. Cochrane Database 2016
Management strategy for children with SRNS

No remission following 8 weeks of initial corticosteroid therapy

ACEi/ARB

KNI (minimum 6 months)

Partial/complete remission

Continue CNI for minimum 12 months

Consider MMF

Consider high-dose corticosteroids

No remission by month 6

Consider enrollment in RCT

Management strategy for children with SRNS and relapse

Relapse after complete remission

- Restart oral corticosteroids (2D)
- Return to previous successful immunosuppressive therapy (2D)
- Start alternative agent to minimize potential cumulative toxicity (2D)

Lombel RM ve ark. Pediatr Nephrol 2013
KDIGO-2012
Mizoribine

Inhibits DNA synthesis in the S phase of the cell cycle
3mg/kg, once daily, before breakfast

*Little data as to whether it is effective in maintaining remission in NS

**Some case series reporting successful treatment with combination therapy using mizoribine, TAC, or plasmapheresis for children with refractory NS in Japan

*van Husen M & Kemper MJ. Pediatr Nephrol 2011
**Galactose**

Oral galactose, a monosaccharide sugar, 0.2 g/kg twice a day inhibits the circulating permeability activity causing FSGS.

**Little evidence** that it improves proteinuria in children with FSGS.

Only a few case reports about partial remission after its usage, as a "nontoxic and adjunctive agent" for SRNS.

Savin VJ et al. Translational Research 2008
Sgambat K et al. Pediatr Nephrol 2013
Kopac M et al. Therapeutic Apheresis and Dialysis 2011
De Smet E et al. NDT 2009
Soluble urokinase receptor (suPAR)

A recently identified circulating factor that may contribute to podocyte injury and proteinuria in FSGS (activates β3 integrin)

suPAR was elevated in 55% to 85% of patients with primary steroid resistant FSGS

Indicative of primary FSGS ??

Novel therapies targeting suPAR?

Meijers B et al. Kidney Int 2014
Synthetic Adrenocorticotropin Analog

*Many decades ago; Adrenocorticotropin (ACTH) injection was used as a therapeutic agent for children with NS (antiproteinuric, lipid lowering, renoprotective)
Later, it has been replaced by cheaper oral steroids

ACTH gel (USA) - 80Ü, sc, twice weekly

**Response to ACTH among adult SRNS patients with FSGS 29%, it may be an alternative treatment option for some patients

T. Mittal T et al. Transplant Proceedings 2015
Abatacept

Cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin fusion protein [CTLA-4-Ig])

Inhibits the T-cell costimulatory molecule B7-1 (CD80)

* 5 patients (2 children- 10 mg/kg, 2 doses) with FSGS; 4 with RTX-resistant recurrent FSGS, and one with steroid-resistant FSGS, whose high proteinuria resolved after abatacept treatment

Abatacept may attenuate β1-integrin activation in podocytes and decrease proteinuria in patients with CD80 positive glomerular disease

Adalimumab

Human monoclonal antibody directed against tumor necrosis factor-α (TNF-α), which triggers an autoimmune response.

Phase I trial by the Novel Therapies for Resistant FSGS (FONT) Study Group

- 10 patients with resistant FSGS (Age: 16.8 +/- 9.0 years)
- 24 mg/m² (max 40mg), sc, every 2 weeks (16 wks, 9 doses)

Well tolerated with no serious side effects, proteinuria decreased by more than 50% in 4 out of 10 patients

Joy MS et al. Am J Kidney Dis 2010
Fresolimumab

- A recombinant, fully human monoclonal antibody
- Inhibits the activity of all isoforms of transforming growth factor (TGF-β)

Phase 1, single-dose study of fresolimumab (1-4 mg/kg) in 16 adults with treatment-resistant FSGS

Follow up; 112 days
1 case complete remission,
2 cases partial remission

Further studies are needed to confirm the efficacy of fresolimumab in FSGS

Trachtman H et al. Kidney Int 2011
Rosiglitazone

- Oral peroxisome proliferator-activated receptor-γ agonists that increase insulin sensitivity
- *Antifibrotic effects in the kidney

The FONT phase 1 trial, 11 children, 3 mg/m²/d, 16 wk

Well tolerated in children with drug resistant FSGS
After 16 months of follow-up;
71% of participants had stable GFR and reduced proteinuria

Potential cardiovascular side effects in older patients with type 2 diabetes

*Kincaid-Smith P et al. Nephrology 2008
Peyser A et al. BMC Nephrol 2010
Stem Cell Therapies

Structural remodeling and functional regeneration of kidney tissue

* Human umbilical mesenchymal stem cells (MSC)

** Autologous stem cell transplantation

*** A 13-year-old patient with recurrent FSGS after kidney transplantation not responding to conventional therapy

3 human allogeneic bone marrow MSC infusions

Improvement of the proteinuria and stabilization of the kidney function leading to discontinuation of the plasmapheresis

** Ruan GP et al. PLoS One 2013
*** Belingheri M et al. Biologicals 2013
If pathogenesis is understood well, many targets in the treatment!!
Conclusion

• Steroid resistance continues to be a major problem
• Currently no known optimal treatment
• Even with the best known treatment options; response rate is 20-50%
• Present treatment options bring also the problems (optimal dose of CNIs, the risk of nephrotoxicity, initiation time of MMF, the role of rituximab, etc)
• Understanding the disease mechanism will assist in the introduction of novel targeted individual approaches in treatment
• Randomized controlled trials should be supported
Steroid

CNIs & MMF

RTX

Novel Agents

to be continued!!
Our current state in treatment of NS!

Never give up!
Please God!
No one asks questions
I can not answer
at the moment!
But, working on it, and... Hope to give good answers in near future!

THANK YOU