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

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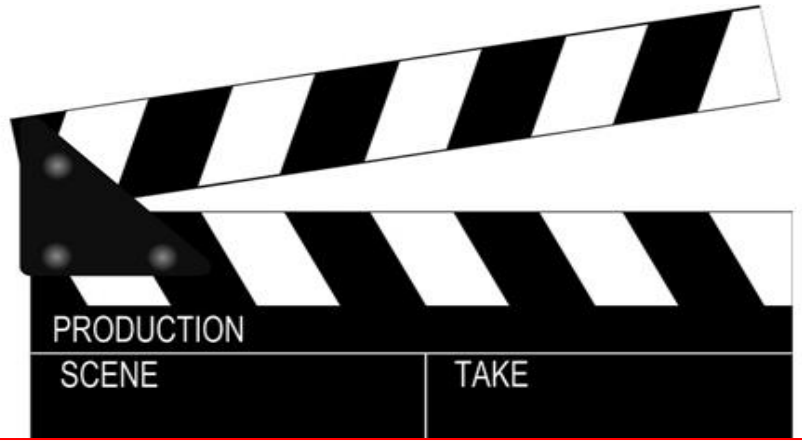
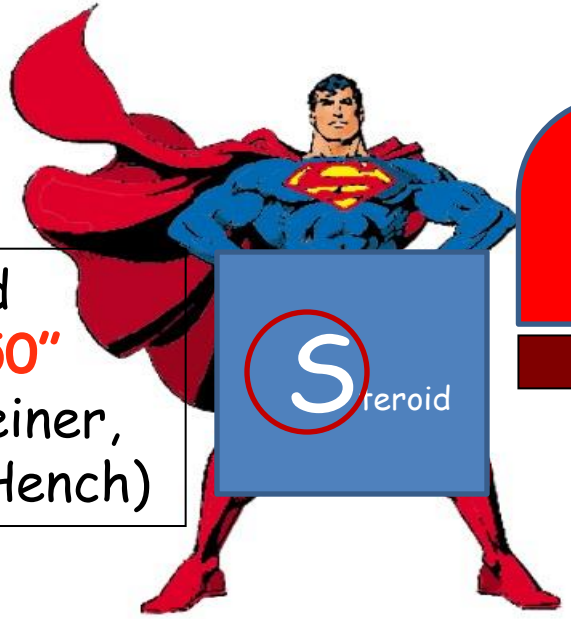
Steroid Sensitive Nephrotic Syndrome



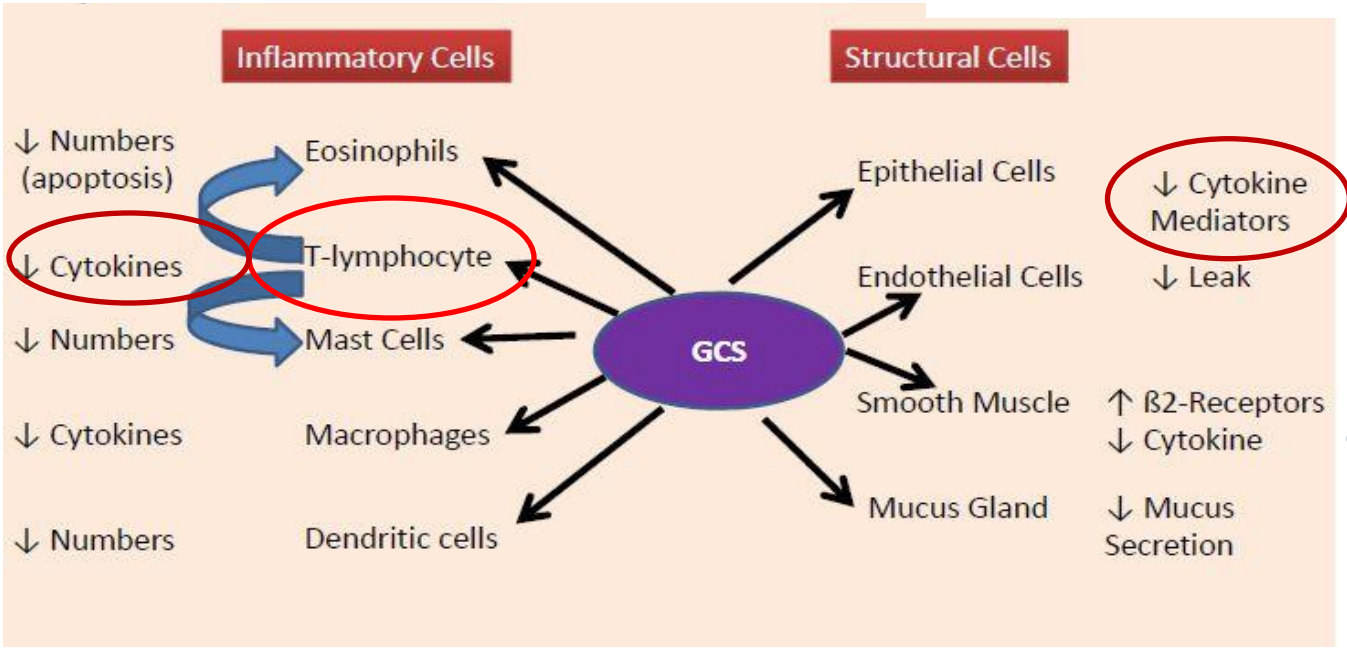
Like an excited movie!- Part 1

1937-Discovered
"Nobel Prize-1950"
(E.Kendall/Wintersteiner,
T. Reichstein , Ph. S. Hench)



NS

CYC
CsA
TAC
MMF
RTX



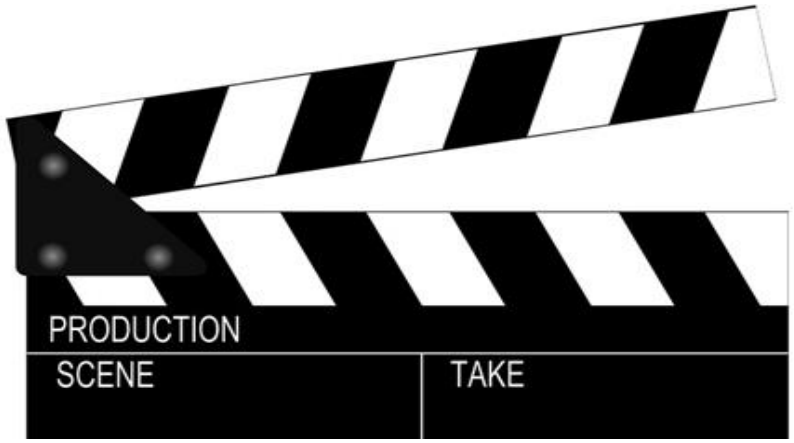
Expectations from the treatment options

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 yaş)- 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

McKinney PA, et al. Pediatr Nephrol 2001

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

Trautmann A et al. Clin J Am Soc Nephrol 2015

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

Abrantes MM, et al. Pediatr Nephrol 2006
Gipson DS , et al. Pediatr Nephrol 2006
Troyanov S , et al. J Am Soc Nephrol 2005

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. J Pediatr. 1981
ISKDC. Lancet. 1974
Tarshish P, et al. Pediatr Nephrol 1996

Kidney Biopsy

Determine the underlying pathology (may dictate therapy)
(for FSGS ; **> 20 glomerül**)
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)

Lombel RM ve ark. Pediatr Nephrol 2013
KDIGO-2012

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
Trautmann A et al. Clin J Am Soc Nephrol 2015

Randomized controlled trials in SRNS

Author	No	Intervention	Control	Duration (mo)	Remission (complete/ partial)	Conclusion
Lieberman &Tejani 1996	24	CyA	Placebo	6	% 100-%17	**CyA** > placebo
Ponticelli C,et al.1993	17	CyA	Supportive therapy	12**	%60-%0	**CyA** > Control
Garin EH, et al. 1998	8	CyA	None	2	%0-%0	No difference
Choudhry S, et al. 2009	41	**TAC**+Pred*	**CYA**+ pred*	12	%86-%75	No difference
Gipson DS, et al. 2011	138	CyA	MMF+dexa metazon	12	%45.8-%33	No difference
ISKDC 1974	31	CPA+ Pred	prednizon	3	%56-%46	No difference
Tarshish P, et al. 1996	53	CPA+ Pred	prednizon	3+12	%50-%57	No difference

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

Medication Protocol	No. of Patients	No. of Periods	Cotreated with RAS Antagonists (%)	Cotreated with Oral Steroids (%)	Treatment Duration (mo)	Response to Therapy	
						Partial Remission N/N_{info} (%)	Complete Remission N/N_{info} (%)
RAS antagonists only	623	950	—	63.3	5.2 (1.9-17.1)	109/531 (20.5)	141/531 (26.6)
Oral steroids only	722	1119	—	—	2.0 (1.4–4.7)	53/567 (9.3)	62/567 (10.9)
Steroid pulses	541	1114	51.0	72.4	0.1 (0.1–0.9)	42/279 (15.1)	25/279 (9.0)
CPH (oral or pulse)	273	336	39.0	92.0	2.5 (1.6–3.0)	11/131 (8.4)	22/131 (16.8)
CNI	806	1210	70.7	89.5	8.3 (3.0–23.0)	153/ (21.6)	65.6% 1/707 (44.0)
MMF	177	219	80.4	71.7	6.7 (3.0-14.9)	19/148 (12.8)	57/148 (38.5)
CNI + MMF	137	167	81.4	76.0	7.7 (3.0-23.9)	26/119 (21.8)	57/119 (47.9)
Rituximab	79	91	87.9	76.9	0.0 (0.0-4.6)	10/66 (15.2)	29/66 (43.9)

Trautmann A et al. Clin J Am Soc Nephrol 2015

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?

*Lieberman KV &Tejani A. J Am Soc Nephrol 1996

**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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Trautmann A et al. Clin J Am Soc Nephrol 2015

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.

MMF

138 (93 children), Primary SRNS and FSGS

MMF + high-dose dexamethasone

Cyclosporine

Complete or partial remission

%33

No significant difference

%46

Gipson DS et al. Kidney Int 2011

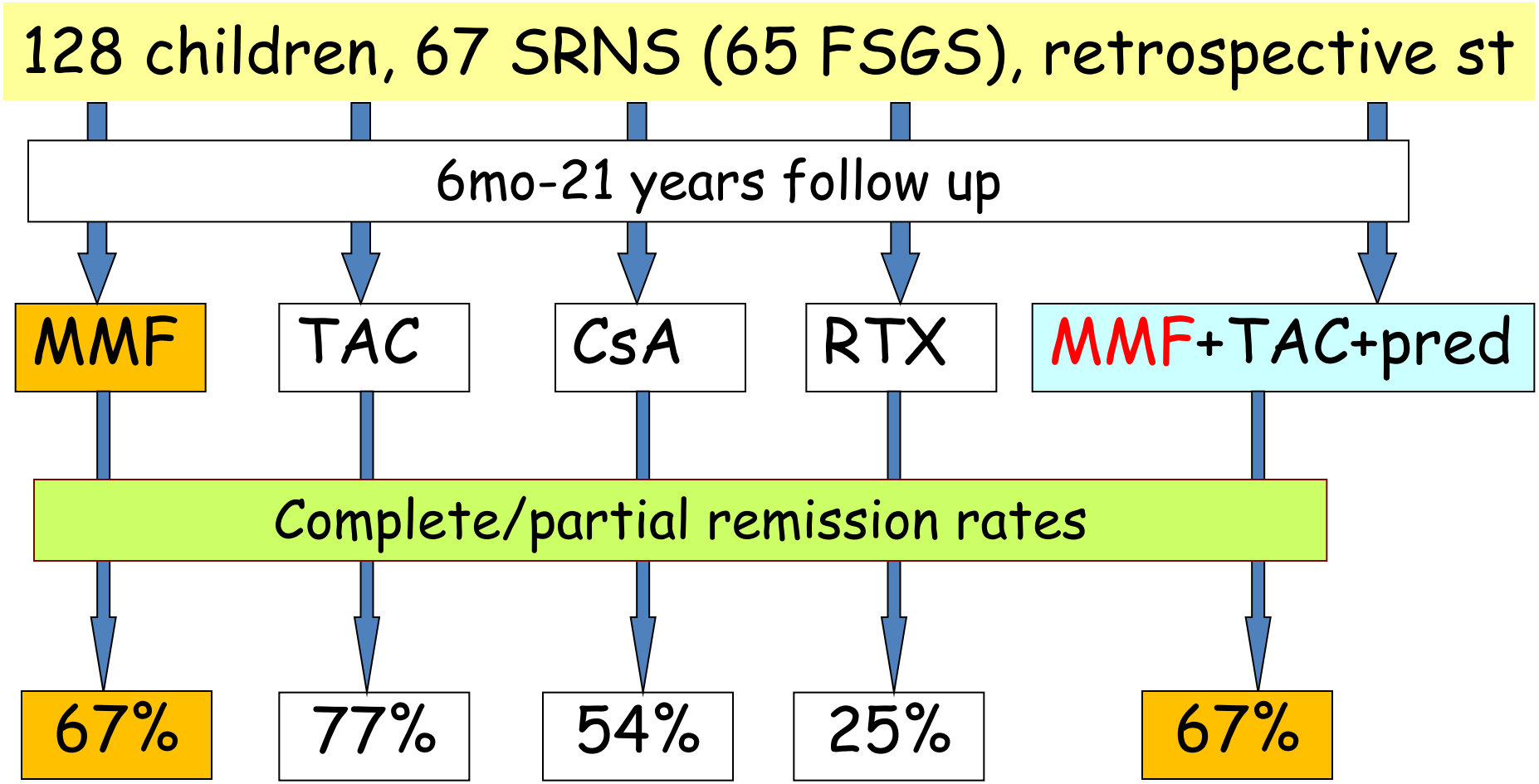
** Observational studies, 42 children, minimum treatment period with MMF; 6 months

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



Kim J et al. Nephron Extra 2014

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51.3%

Trautmann A et al. Clin J Am Soc Nephrol 2015

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	Dexamethasone
33.3% complete remission 14.3% partial remission	35.1% complete remission 12.3% partial remission

Hari P et al. Indian Pediatr 2004

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24.1%

Trautmann A et al. Clin J Am Soc Nephrol 2015

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
Tarshish P et al. Pediatr Nephrol 1996
+Gipson DS et al. Kidney Int 2011
Garin EH et al. Am J Dis Child 1988

Lieberman KV &Tejani A. J Am Soc Nephrol 1996
Ponticelli C et al. Kidney Int 1993
*Ehrich JH et al. NDT 2007

Alkylating agents

2 RCTs, 84 children with SRNS

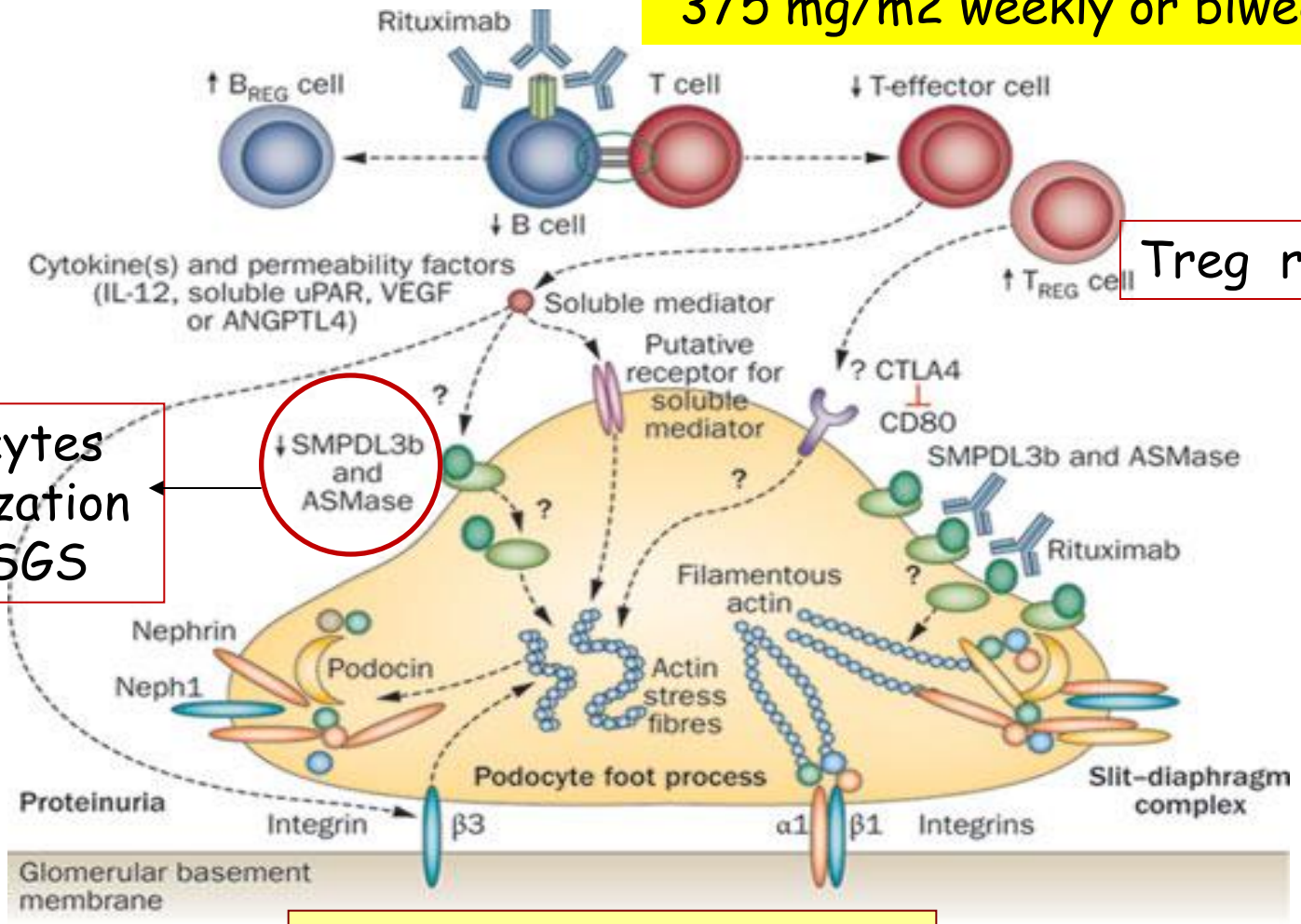
Cyclophosphamide + prednisone therapy was not superior to prednisone

KDIGO- Cyclophosphamide **should not be used** in children with SRNS

ISKDC. Lancet. 1974
Tarshish P et al. Pediatr Nephrol 1996
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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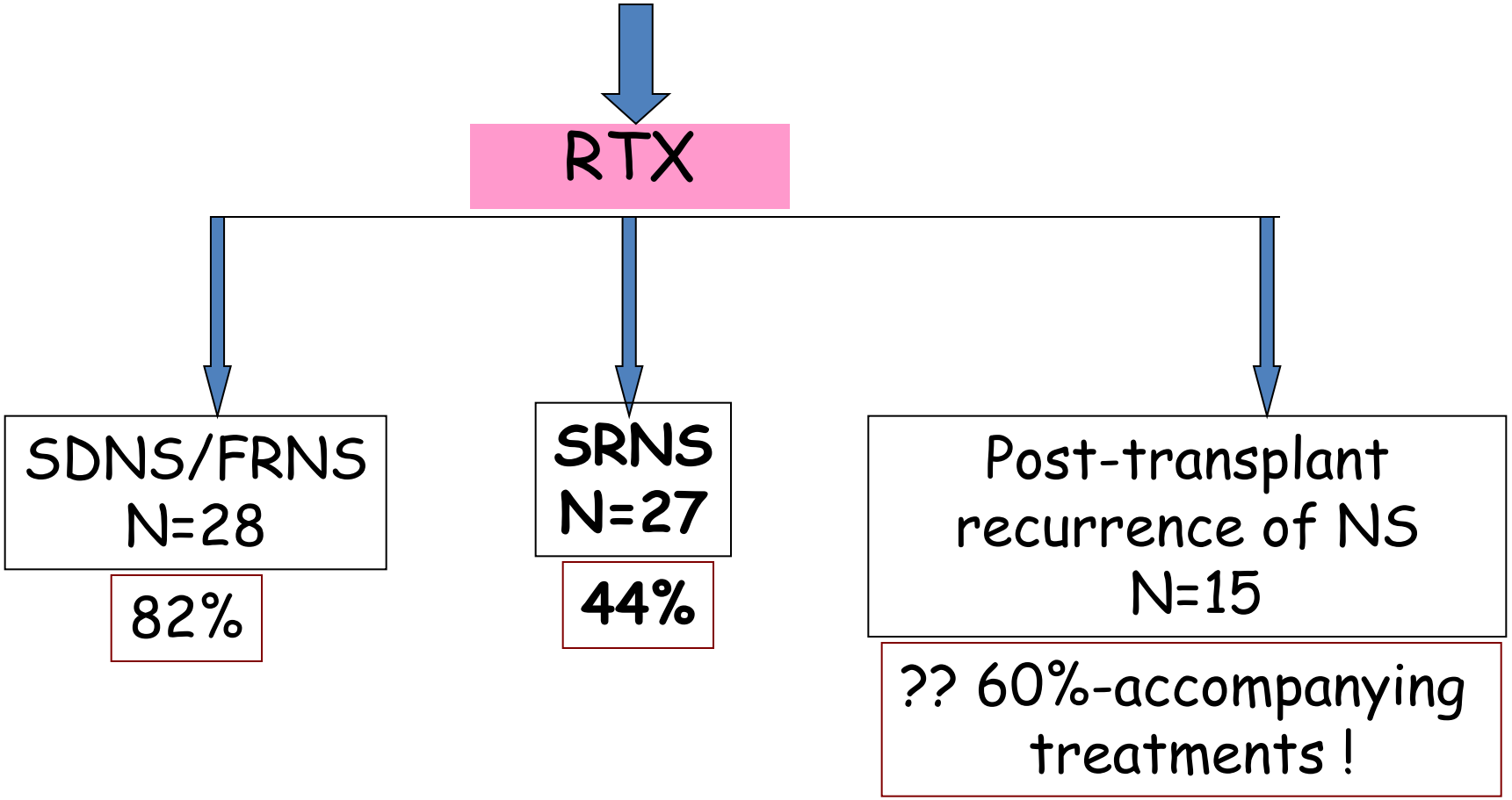
Rituximab	79	91	87.9	76.9	0.0 (0.0-4.6)	10/66 (15.2)	29/66 (43.9)

59.1%

Trautmann A et al. Clin J Am Soc Nephrol 2015

A questionnaire filled by members of the IPNA;



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

*Gulati A et al. Clin J Am Soc Nephrol 2010
*Prytula A et al. Pediatr Nephrol 2010
Ravani P et al. Clin J Am Soc Nephrol 2016
Ahn YH et al. Pediatr Nephrol 2014

Cochrane Database-2016

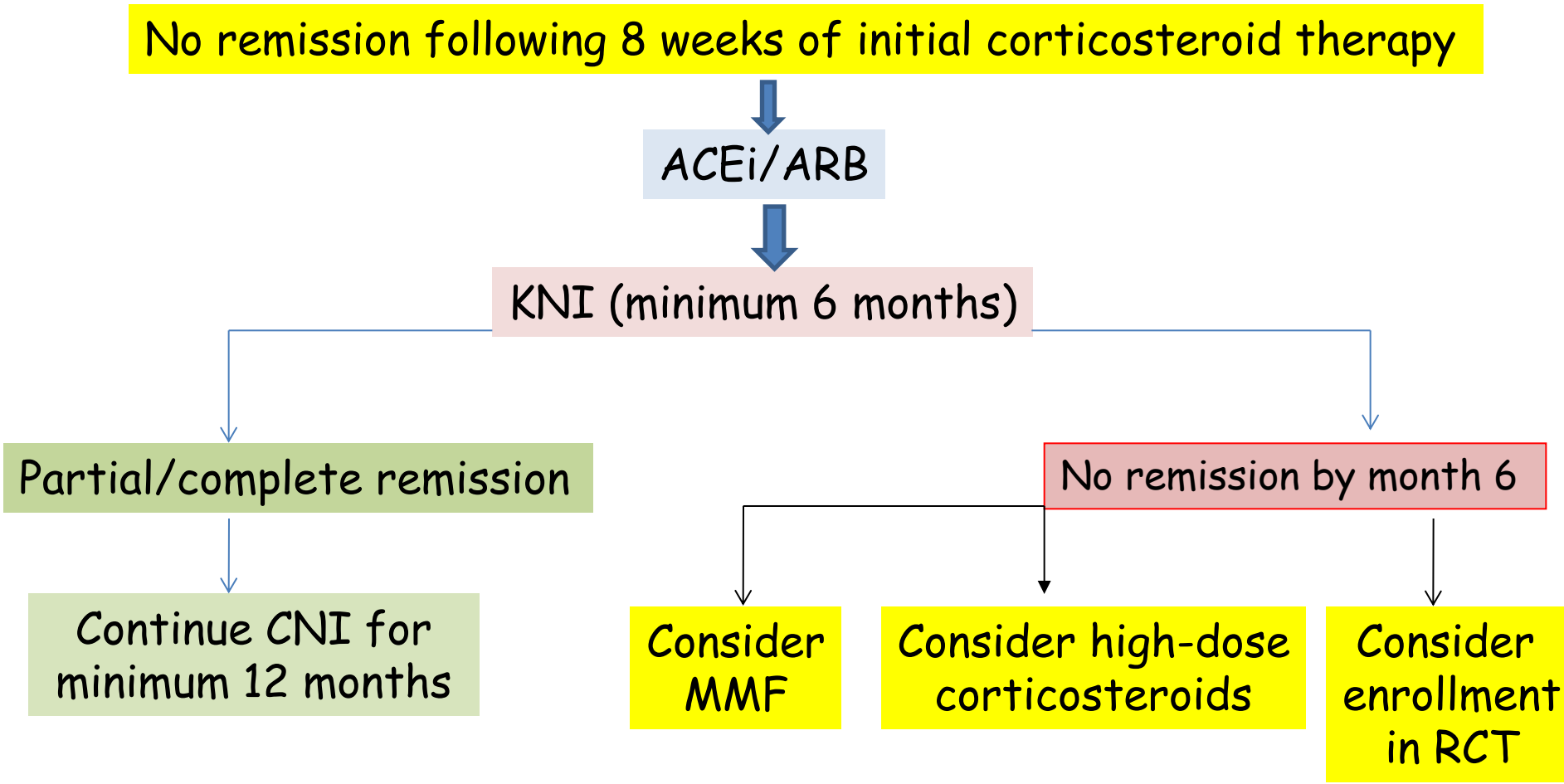
No significant differences between;

- **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



Lombel RM ve ark. Pediatr Nephrol 2013
KDIGO-2012

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
**Aizawa-Yashiro T et al. Pediatr Nephrol 2011
** Imaizumi T et al. Pediatr Nephrol 2007

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

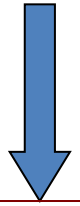
Only a few case reports about partial remission after its usage, as a "**nontoxic and adjunctive agent**" for SRNS

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?

Wei C et al. J Am Soc Nephrol 2012
Bock ME et al. Clin J Am Soc Nephrol 2013
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

*Rapoport M et al. J Am Med Assoc 1951
T. Mittal T et al.Transplant Proceedings 2015
**Hogan J et al.Clin J Am Soc Nephrol 2013
Malaga-Dieguez L et al.Adv Chronic Kidney Dis 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

Yu C-C et al. N Engl J Med 2013

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

16 months follow up

- 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/m^2/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
Joy MS et al. Clin J Am Soc Nephrol 2009
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

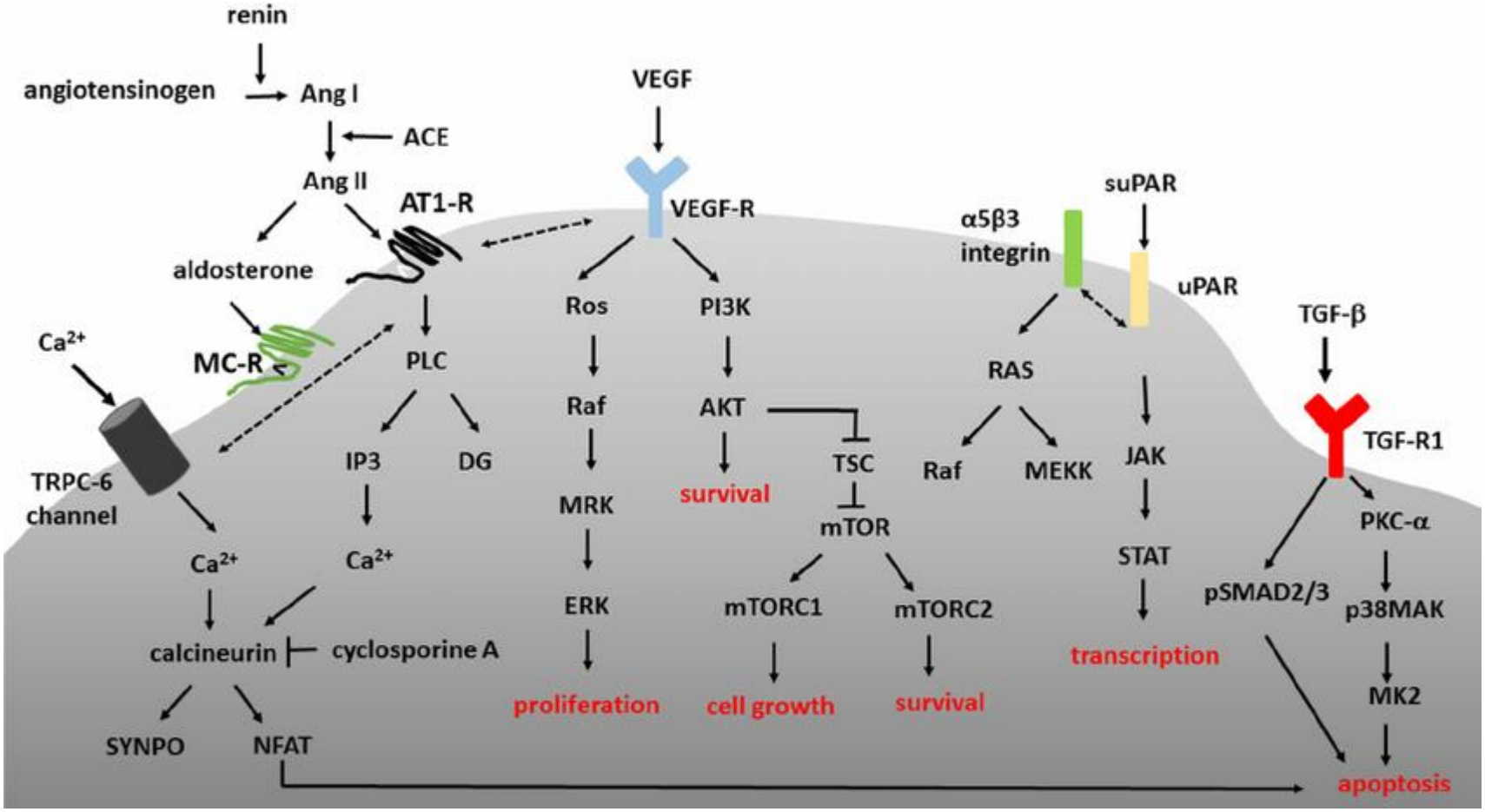
→ 3 human allogeneic bone marrow MSC infusions

↓

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

*Ma H et al. Am J Med Sci 2013
**Ruan GP et al. PLoS One 2013
***Belingheri M et al. Biologicals 2013

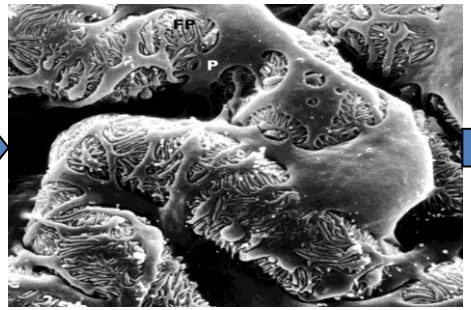
If pathogenesis is understood well, many targets in the treatment !!



Janina Müller-Deile & Mario Schiffer. Pediatr Nephrol 2016

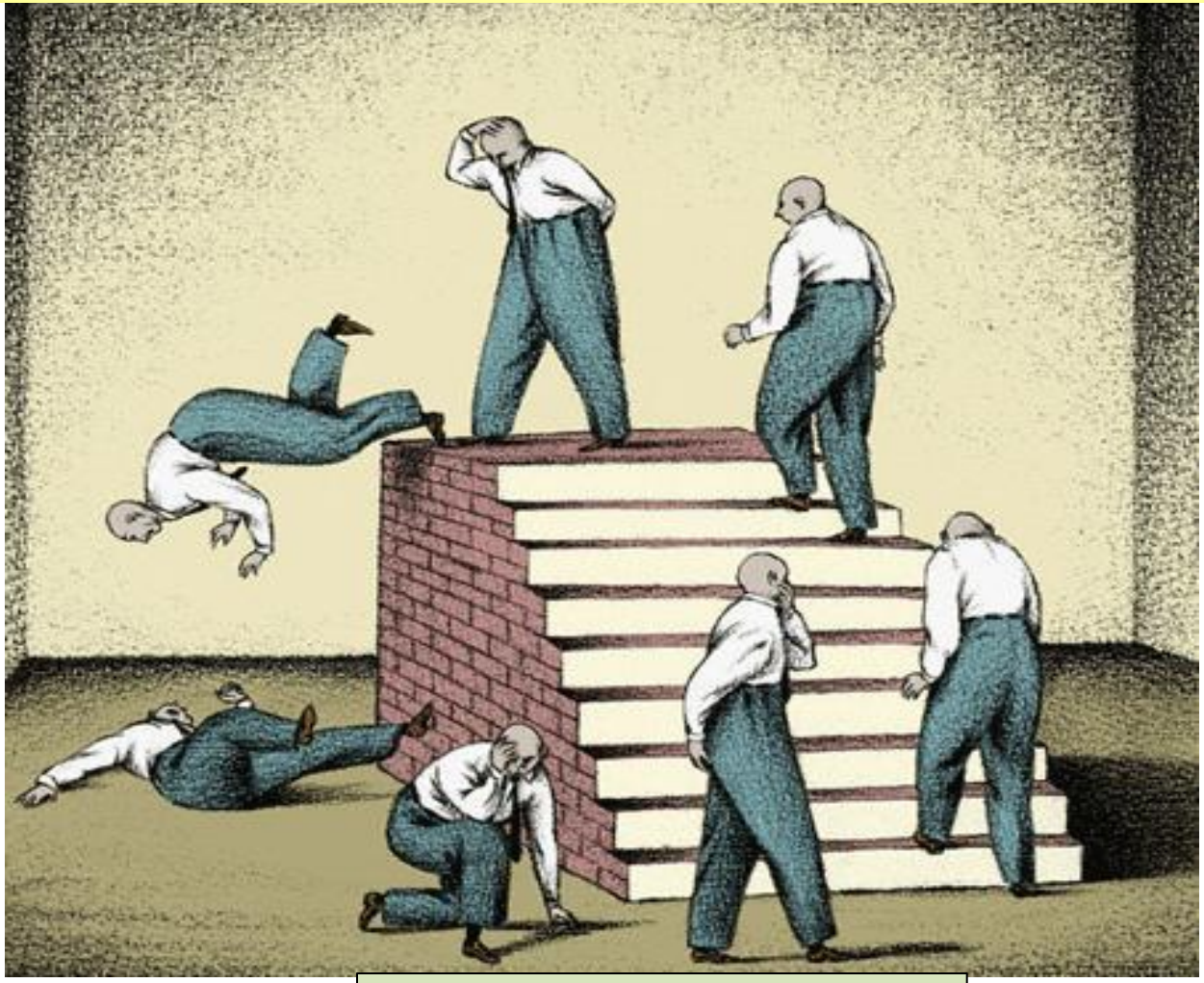
Conclusion

- 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



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!
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But, working on it, and...
Hope to give good answers
in near future!

THANK YOU