ERKNet
The European
Rare Kidney Disease
Reference Network

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ERKNet
Advanced Webinars on Rare Kidney Disorders

Date: 28 January 2020

Update on the treatment of SSNS

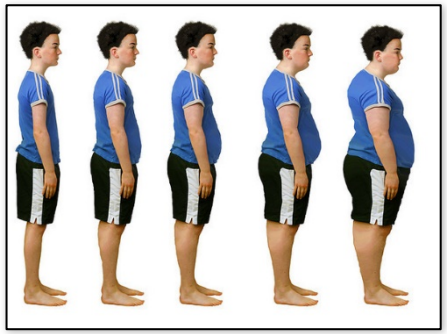
Speaker: Francesco Emma (Rome Bambino Gesù Children`s Hospital, Italy)

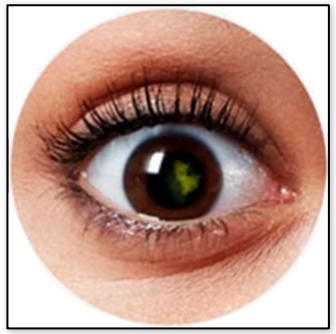
Moderator: Elena Levtchenko (Leuven University Hospital, Belgium)

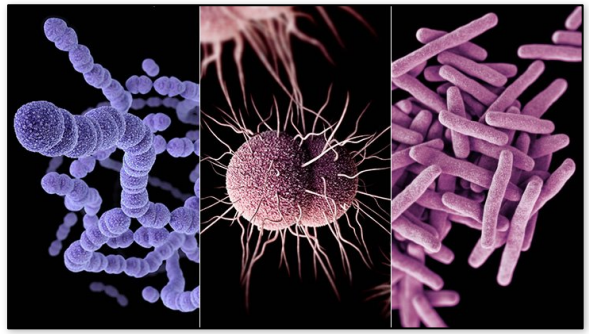
Recent progresses in the treatment of SSNS

No major developments, but we have learned how to use better established therapies

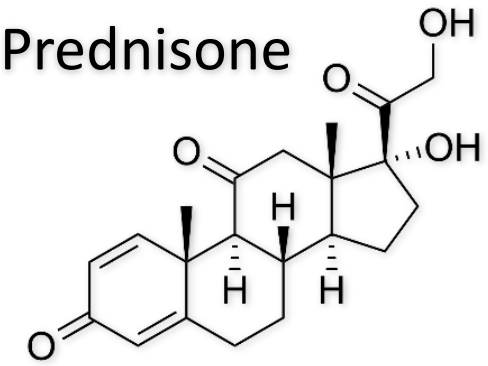
Steroid toxicity

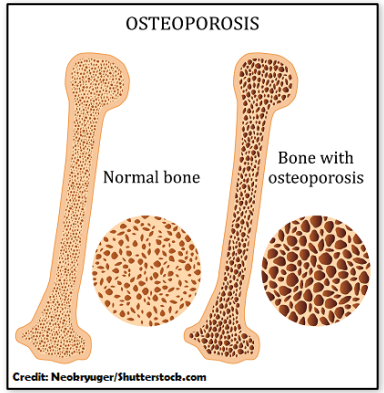


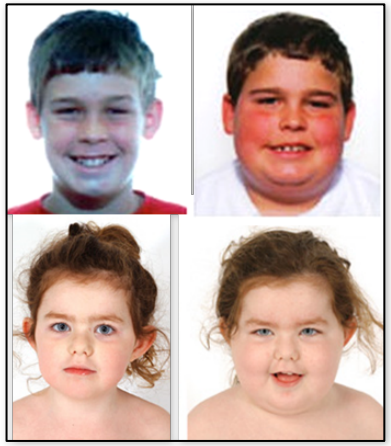


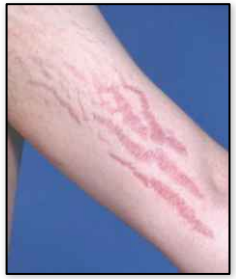


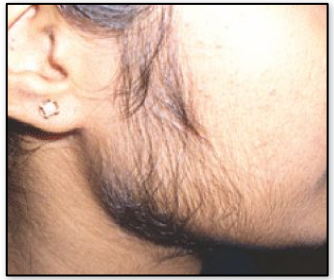
Prednisone

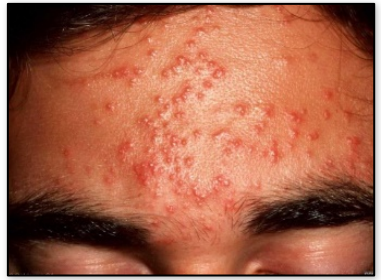




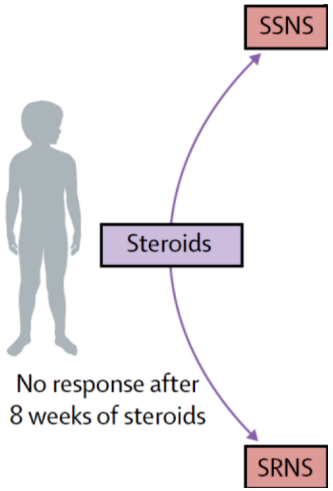






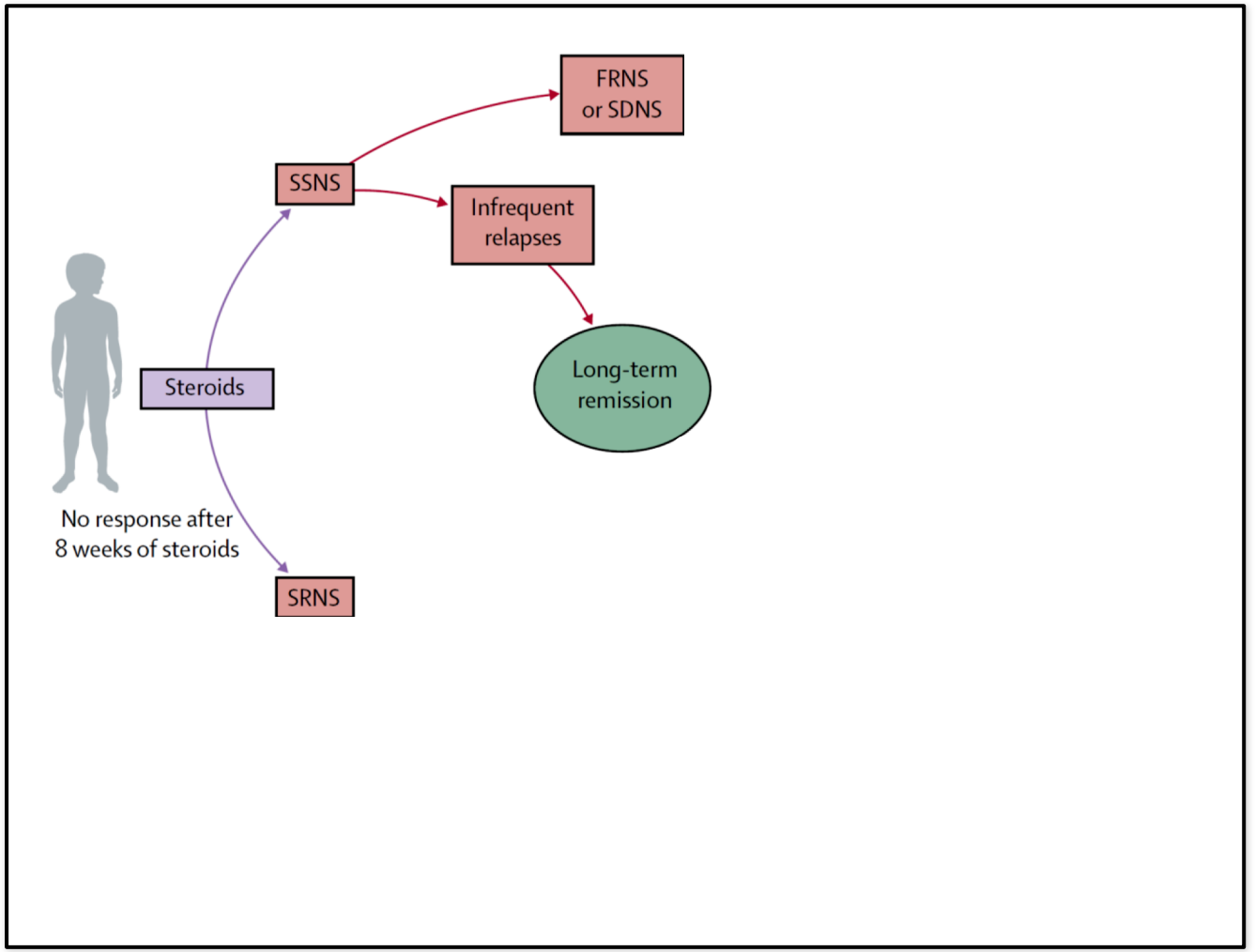


Idiopathic nephrotic syndrome in children



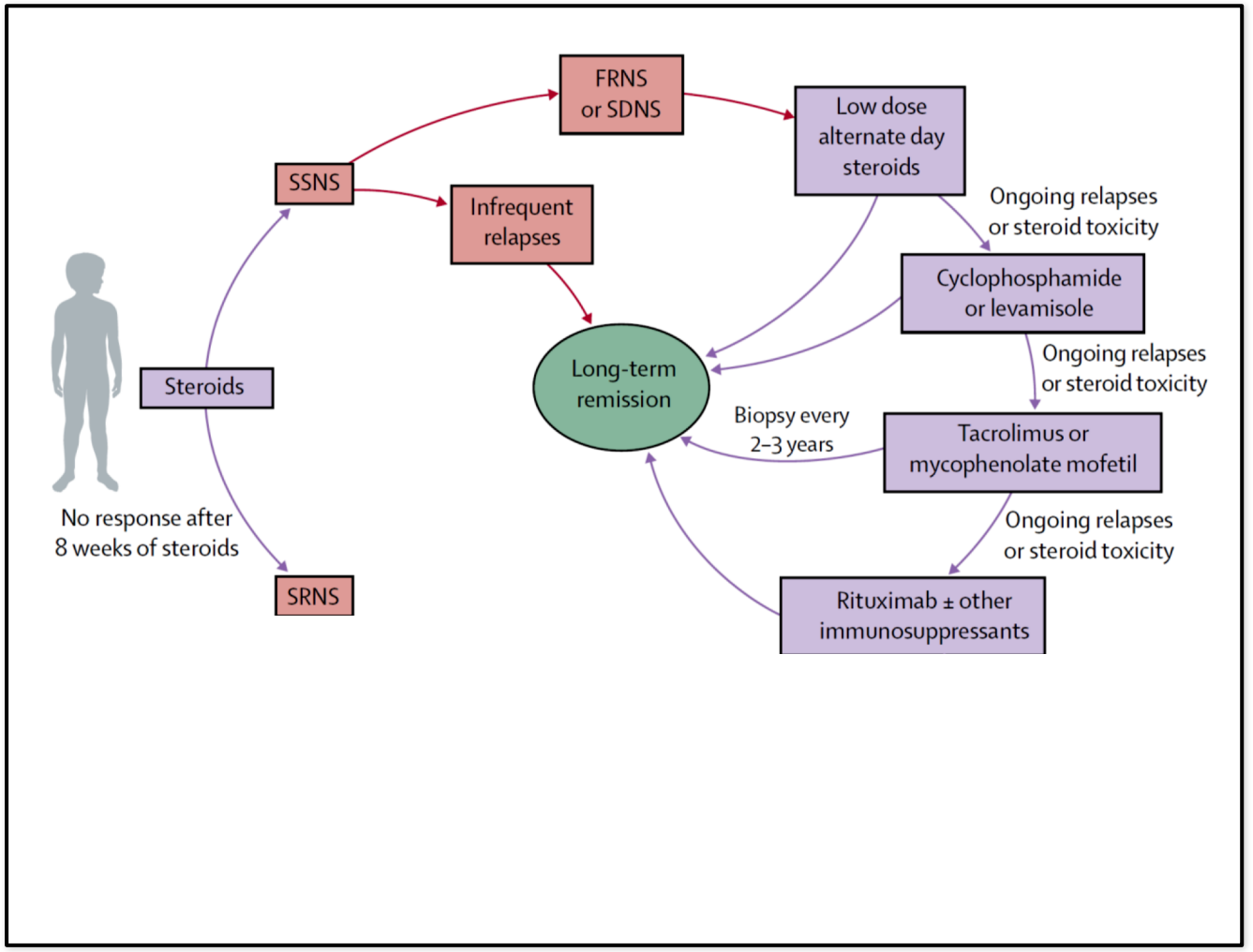
Noone et al, Lancet 2018

Idiopathic nephrotic syndrome in children



Noone et al, Lancet 2018

Idiopathic nephrotic syndrome in children



Noone et al, Lancet 2018

Treatment protocols for SSNS in children: initial presentation

	International Study of Kidney Disease in Children (ISKDC)[61]	Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)[2]	Haute Autorité de Santé (France)[62]	Italian Society for Pediatric Nephrology (SINePe)[63]	KDIGO Glomerulonephritis Guidelines[1]	Hospital for Sick Children (Toronto, Canada)[11]
Year of publication	1970	1988	2008	2017	2012	2016
Initial dose and duration	60 mg/m² per day × 4 weeks	60 mg/m² per day × 6 weeks (maximUm dose 80 mg)	60 mg/m² per day × 4 weeks (maximum dose 60 mg)	60 mg/m² per day × 6 weeks (maximum 60 mg in single or 2 divided doses)	60 mg/m² per day or 2 mg/kg per day × 4–6 weeks (maximum 60 mg)	60 mg/m² per day × 6 weeks (maximum 60 mg in single morning dose)
Subsequent dose and tapering	4 weeks of 40 mg/m² per alternate day but given on 3 consecutive days out of a week	40 mg/m² per alternate day × 6 weeks (maximum dose 60 mg)	60 mg/m² per alternate day × 8 weeks (maximum 60 mg) followed by a 15 mg/m² per alternate day × 15 days and continue to wean. In addition, 3 methylprednisolone pulses if proteinuria persists after 1 month of daily prednisone therapy	40 mg/m² per alternate day × 6 weeks (single dose; maximum 40 mg) without tapering	40 mg/m² per alternate day or 1·5 mg/kg/alternate day (maximum 40 mg) × 6–8 weeks (at least 12 weeks) and continued for 2–5 months with tapering	40 mg/m² per alternate day × 6 weeks (maximum 60 mg), 30 mg/m² per alternate day × 8 days (maximum 30 mg), 20 mg/m² per alternate day × 8 days (maximum 20 mg), 10 mg/m² per alternate day × 12 days (maximum 10 mg)

Noone et al, Lancet 2018

Treatment protocols for SSNS in children: relapses

	International Study of Kidney Disease in Children (ISKDC)[61]	Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)[2]	Haute Autorité de Santé (France)[62]	Italian Society for Pediatric Nephrology (SINePe)[63]	KDIGO Glomerulonephritis Guidelines[1]	Hospital for Sick Children (Toronto, Canada)[11]
Year of publication	1970	1988	2008	2017	2012	2016
Starting dose and duration	..	..	60 mg/m² per day until urine protein is negative for 6 days	60 mg/m² (max 60 mg in a single or 2 divided doses) until urine protein is negative for 5 days	60 mg/m² per day or 2·0 mg/kg per day (maximum of 60 mg/day) until urine is negative for 3 days	60 mg/m² per day until urinary protein is trace or negative for 5 consecutive days
Follow-up dose and duration	..	..	60 mg/m² per alternate day × 4 weeks, 45 mg/m² per alternate day × 4 weeks, 30 mg/m² per alternate day × 4 weeks, 15 mg/m² per alternate day × 4 weeks	40 mg/m² per alternate day (max 40 mg) × 4 weeks	40 mg/m² or 1·5 mg/kg/ alternate day (maximum 40 mg) × 4 weeks (minimum)	60 mg/m² per alternate day × 8 days (maximum 60 mg/day), 50 mg/m² per alternate day × 8 days (maximum 50 mg/day), 40 mg/m² per alternate day × 8 days (maximum 40 mg/day), 30 mg/m² per alternate day × 8 days (maximum 30 mg/day), 20 mg/m²/alternate day × 8 days (maximum 20 mg/day), 10 mg/m² per alternate day × 8 days (maximum 10 mg/day)

Noone et al, Lancet 2018

Question 1

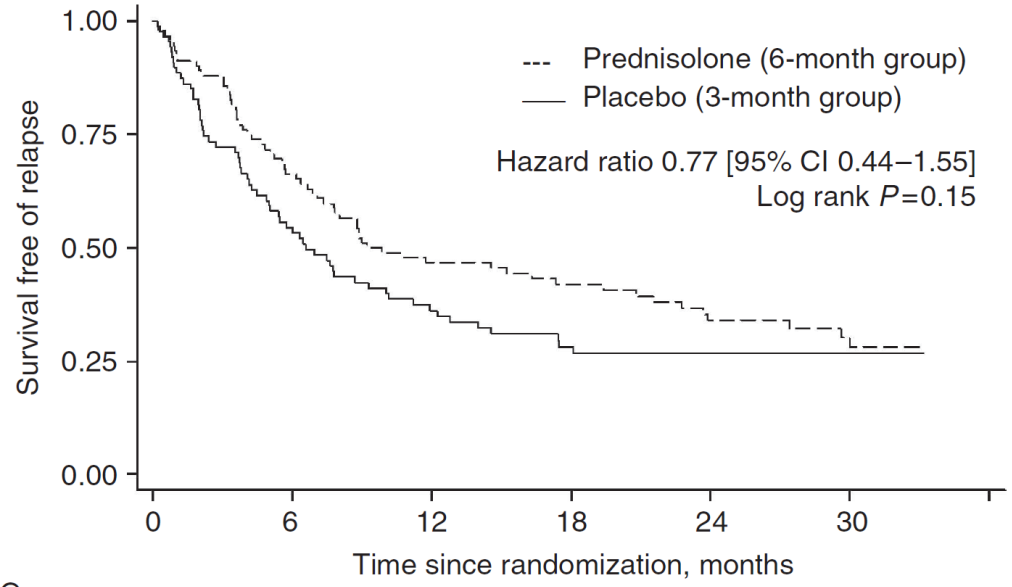
How does the intensity of the initial steroid treatment affects disease outcome at 24 months?

1. higher PDN dose allow to decrease the cumulative dose of PDN
2. lower PDN dose allow to decrease the cumulative dose of PDN
3. the initial PDN dose has little impact on the outcome at 24 months
4. none of the above is correct

Evolution according to the initial therapy 3 vs 6 months

Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome

Aditi Sinha[1], Abhijeet Saha[2], Manish Kumar[3], Sonia Sharma[1], Kamran Afzal[4], Amarjeet Mehta[5], Mani Kalaivani[6], Pankaj Hari[1] and Arvind Bagga[1]



Group						
6-Month	92	61 (31)	43 (18)	35 (4)	25 (6)	15 (2)
3-Month	88	47 (39)	30 (15)	20 (6)	17 (1)	12 (0)

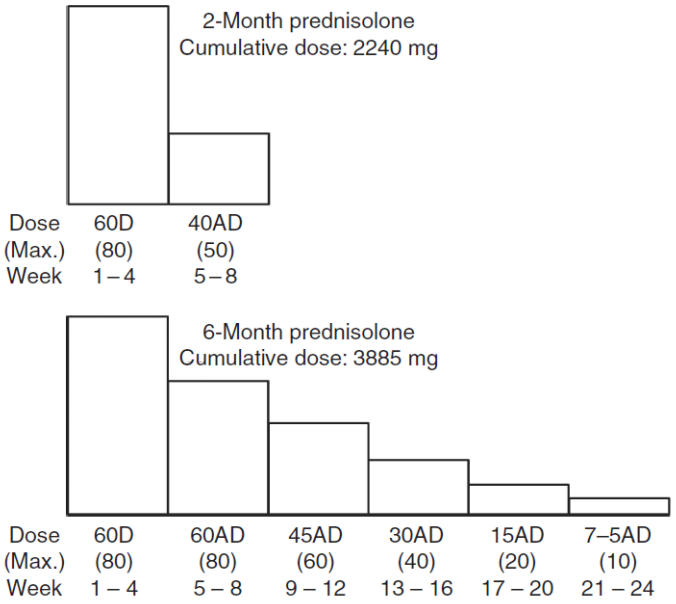
Relapse-free survival.
The proportions with sustained remission in patients treated for 6 months and 3 months were similar at 12 months (46.7 vs. 36.2%), at 24 months (34.1 vs. 26.8%), and at last follow-up (28.4 vs. 26.8%).

Kidney International (2015)

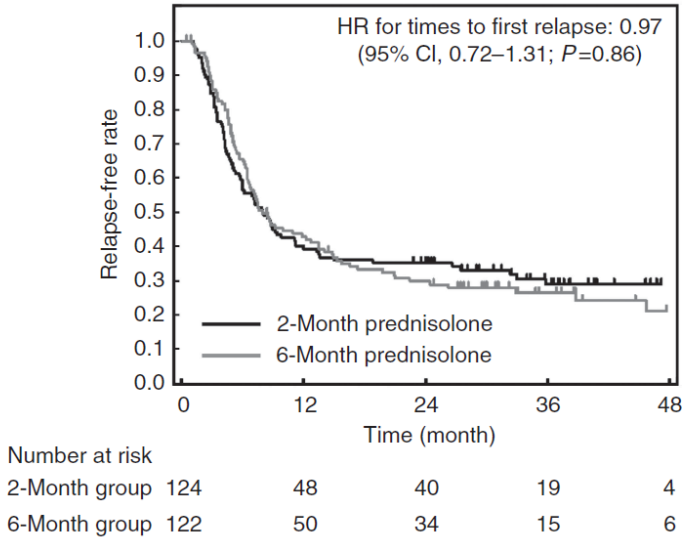
Evolution according to the initial therapy 2 vs 6 months

A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment

Norishige Yoshikawa[1], Koichi Nakanishi[1], Mayumi Sako[2], Mari S. Oba[3], Rintaro Mori[4], Erika Ota[4], Kenji Ishikura[5], Hiroshi Hataya[5], Masataka Honda[5], Shuichi Ito[6], Yuko Shima[1], Hiroshi Kaito[7], Kandai Nozu[7], Hidefumi Nakamura[2], Takashi Igarashi[8], Yasuo Ohashi[9] and Kazumoto Iijima[7]; for the Japanese Study Group of Kidney Disease in Children[10]



Kaplan–Meier estimates of time to first relapse.



Kidney International (2015)

Treatment at disease onset

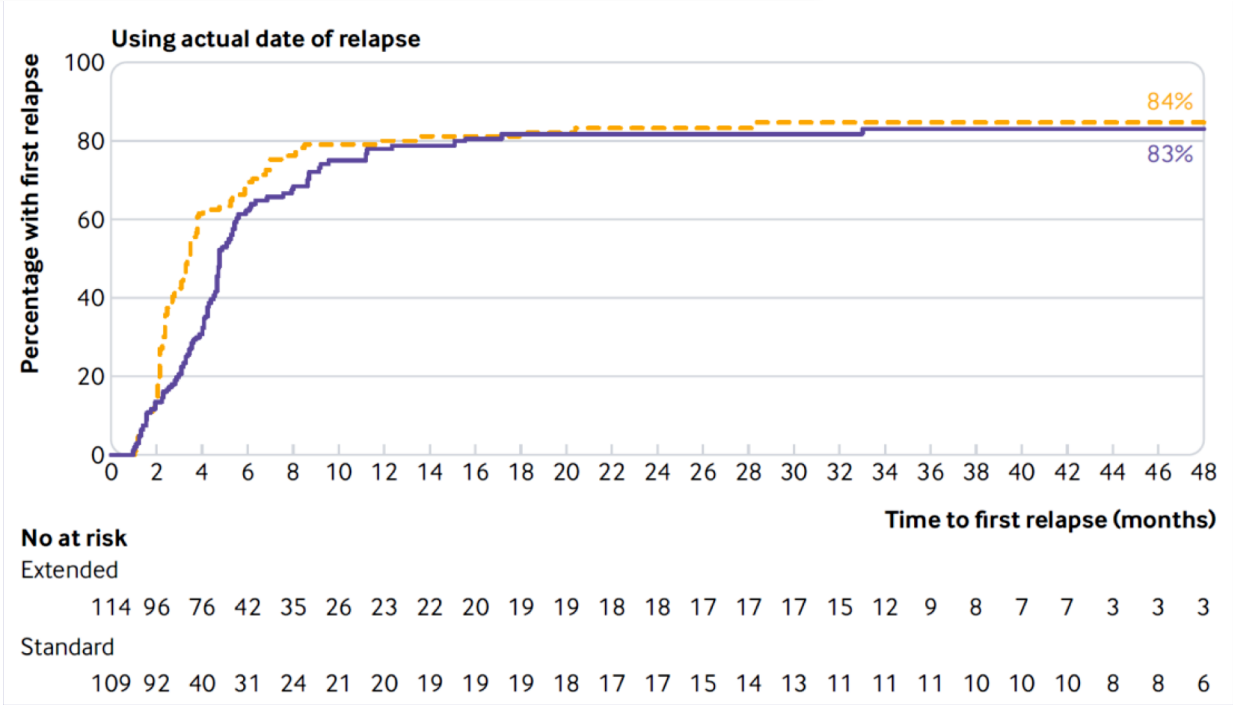
Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation

Nicholas J A Webb,[1,2] Rebecca L Woolley,[3] Tosin Lambe,[4] Emma Frew,[4] Elizabeth A Brettell,[3] Emma N Barsoum,[3] Richard S Trompeter,[5] Carole Cummins,[6] Jonathan J Deeks,[3,7] Keith Wheatley,[8] Natalie J Ives,[3] On behalf of the PREDNOS Collaborative Group

BMJ 2019

- 237 children aged 1-14 years
- first episode of SSNS
- Placebo-controlled double blind RCT

16 vs. 8 week course of prednisolone
(total dose 3150 mg/m^2 vs. 2240 mg/m^2)



PDN therapy at onset has no impact on long-term outcome

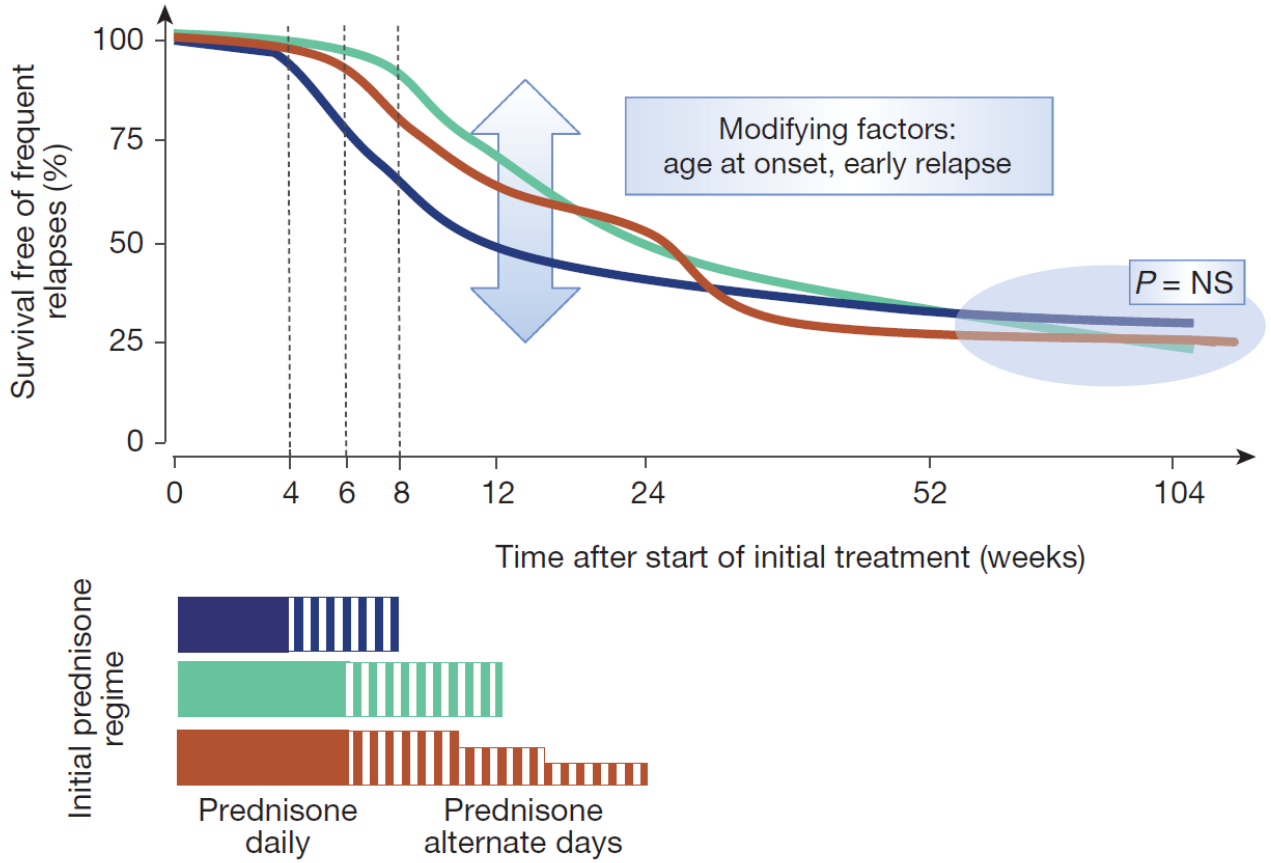


Figure 1 | Lack of effect of extending initial prednisone treatment on long-term freedom from frequent relapses. NS, not significant.

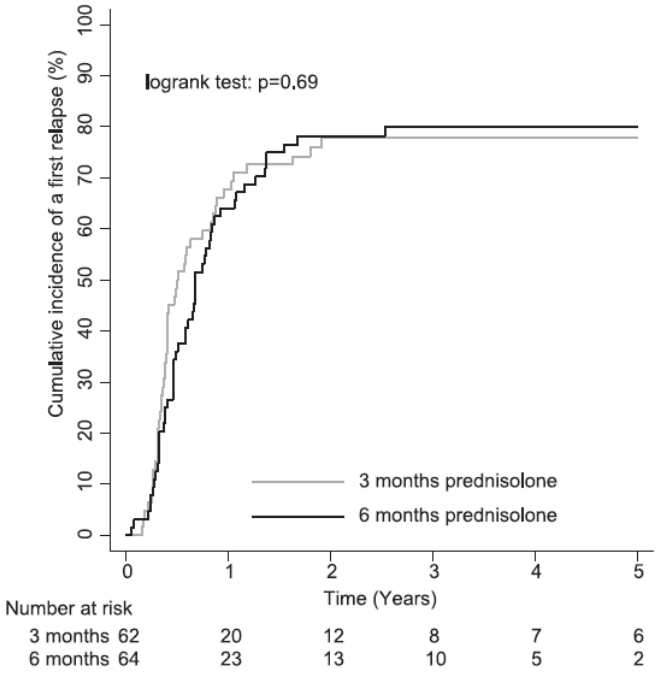
Hoyer P. Kidney Int 2015

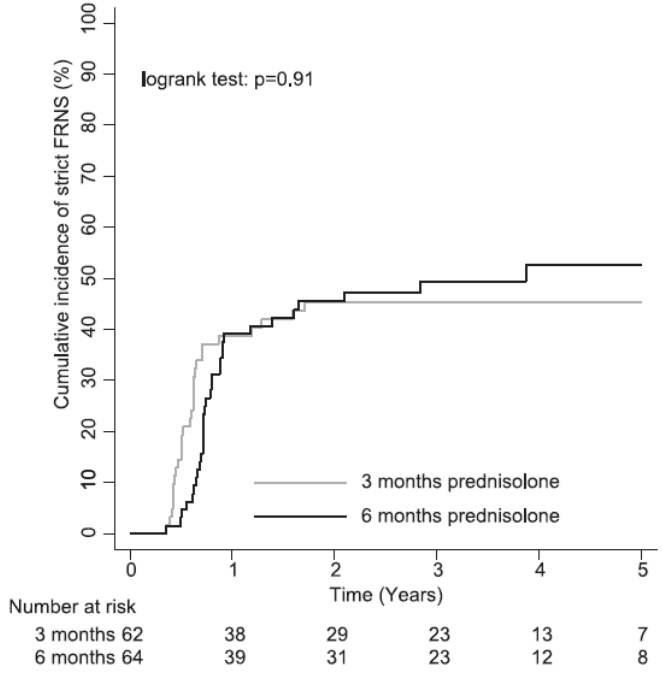
PDN tapering or not?

Extending Prednisolone Treatment Does Not Reduce Relapses in Childhood Nephrotic Syndrome

Nynke Teeninga,* Joana E. Kist-van Holthe,† Nienske van Rijswijk,* Nienke I. de Mos,‡ Wim C.J. Hop,§ Jack F.M. Wetzels,‖ Albert J. van der Heijden,* and Jeroen Nauta*

week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24	cumulative dose
3 months prednisolone	60 D		60 D				40 AD						placebo AD			3360
6 months prednisolone	60 D		50 D				40 AD				20 AD				10 AD	3320-3710





Teeninga et al, JASN 2012

Steroid sparing agents in SDNS and FRNS

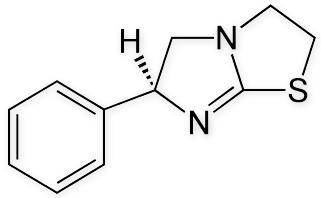
Drug	Efficacy	Indication	Comments
Cyclophosphamide	+++	FRNS/SDNS	Severe cases often relapse rapidly
Levamisole	+++	FRNS	Few RCTs / ANCA-associated disease
Calcineurin inhibitors	+++++	SDNS	Side effects
Mofetil mycofenolate	++++	FRNS/SDNS	Often need to use high doses (> 600 mg/m^2)
Rituximab	++++	FRNS/SDNS	May compromise immunological memory

Question 2

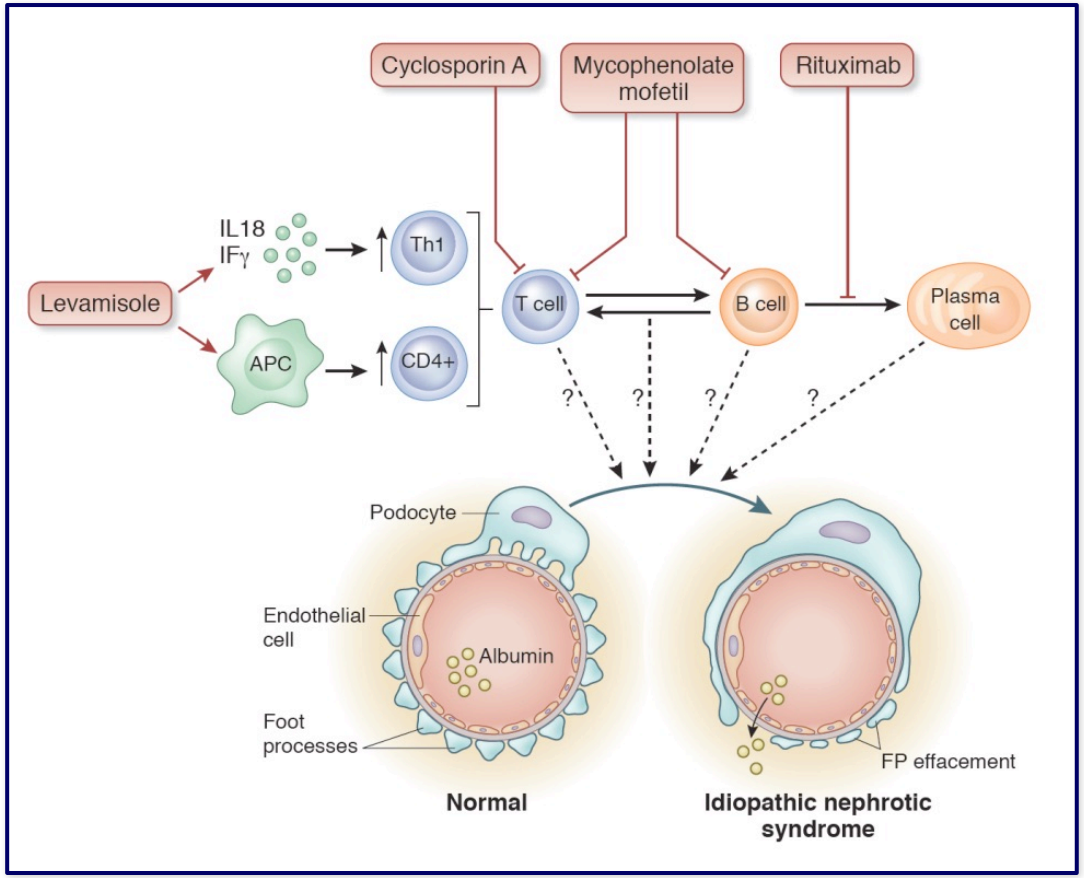
How does levamisole works?

1. inhibit humoral immune responses
2. decreases PMN cells survival
3. has an indirect effect on T cells
4. all of the above are correct

Levamisole



- Anti-helminthic agent
- Immunomodulatory properties:
  - enhances humoral immune response
  - enhances PMN cells survival
  - stimulates chemotaxis
  - macrophage activation
  - indirect effect on T cells via:
    - activation of dendritic cells → CD4 pos T-cells
    - interleukin 18 and interferon γ → Th1
- Historically used for:
  - solid tumors
  - immunological conditions
    (oral aphtous ulcers, Behcet syndrome, nephrotic syndrome)
- Withdrawn from the market in in most western countries
- Used in several under-resourced countries (cheap!)



Vivarelli and Emma, Kidney Int 2019

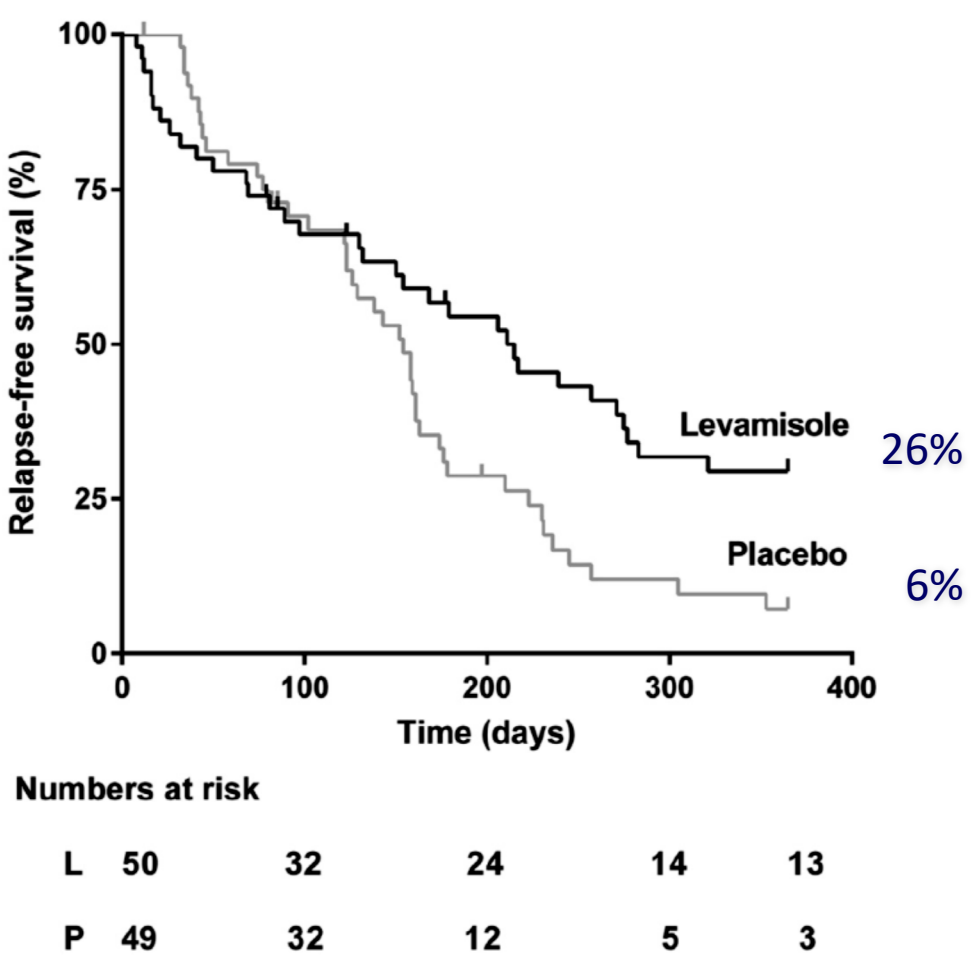
Levamisole

A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome

see commentary on page 310

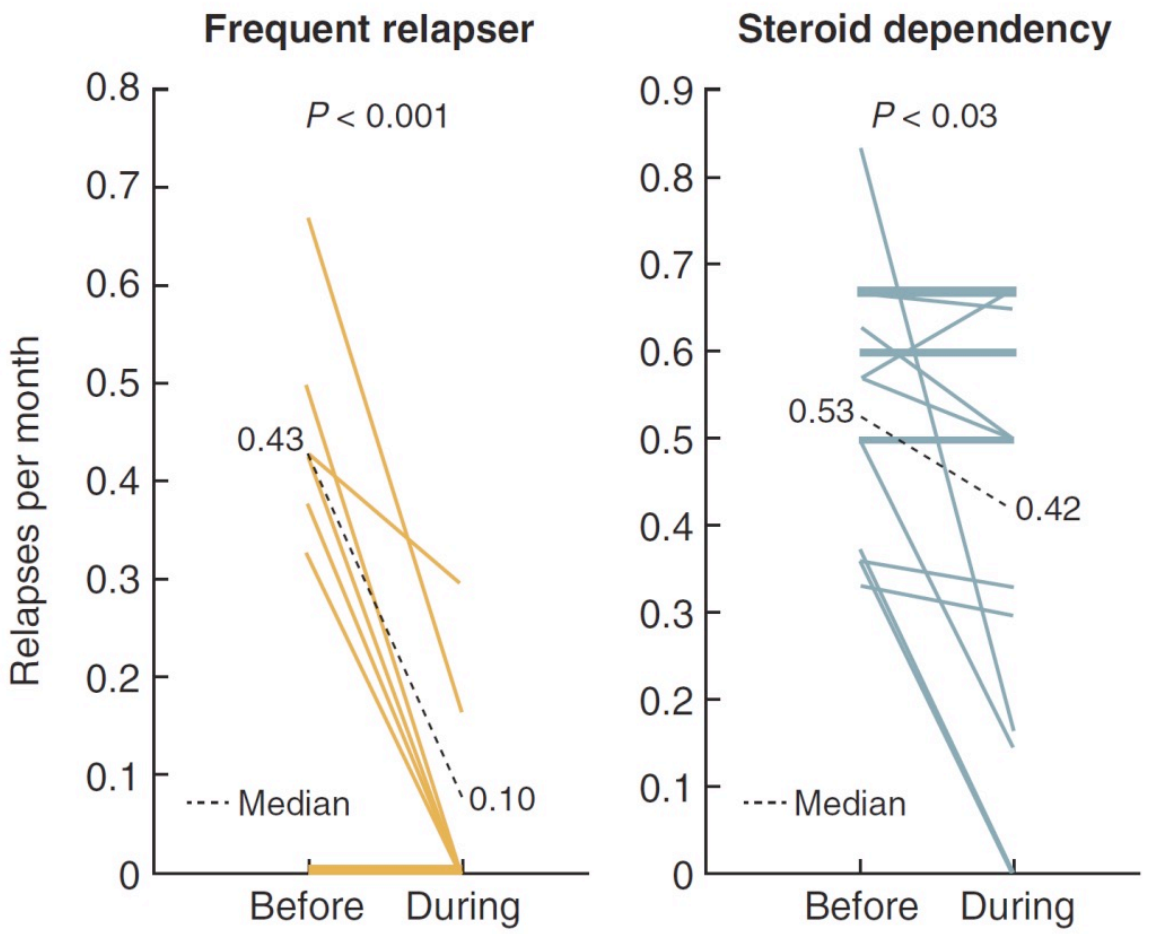
OPEN

- Multicentric, placebo controlled RCT
- 99 children with FRNS/SDNS treated for 12 months
- Good safety profile
  - 4 cases of non-symptomatic neutropenia
    - ✓ 2 resolved spontaneously
    - ✓ 2 resolved after discontinuation
  - 1 case of ANCA-associated arthritis
- Subgroup analysis: higher effectiveness in Indian children
  - India: 58% FRNS
  - Europe centers: 11% FRNS



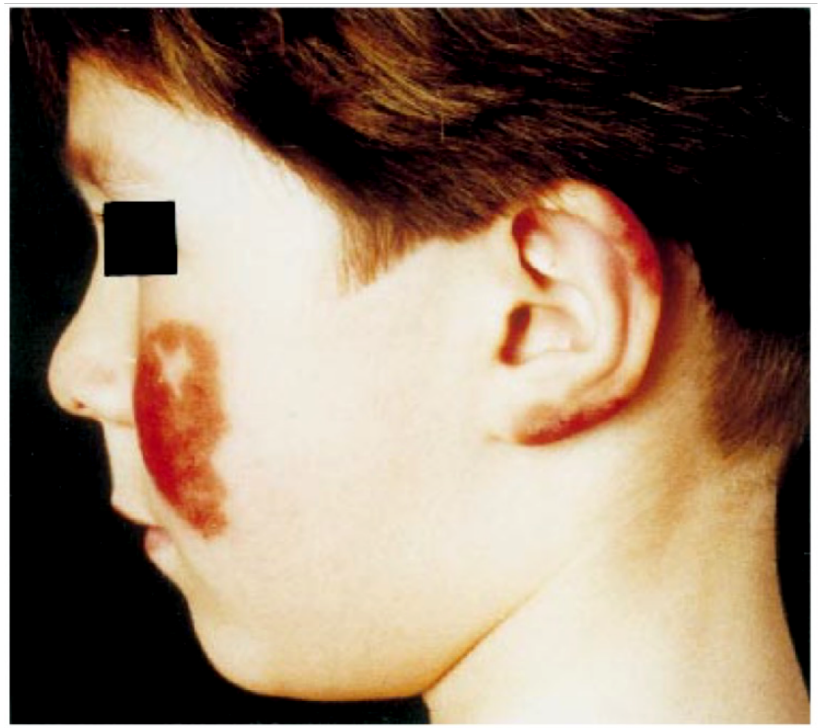
Gruppen et al, Kidney Int 2018

Candidates to levamisole therapy



Kemper and Neuhaus, Kidney Int 2018

ANCA-associated disease under levamisole therapy



Rongioletti et al, Br J Dermatol 1999

- Some children develop arthritis and/or cutaneous vasculitis
- On average of 2 years after starting levamisole
- ANCA positivity
- Reversible upon treatment discontinuation + steroids
- ANCA may persist for several months/years

<u>Our recent experience</u>:

- Monitoring of ANCA every 6 months
- 25 children treated for 2-4 years
- 5 (20%) developed ANCA, usually after >2 years
- Levamisole was always stopped: none developed symptoms

Levamisole vs MMF for FRNS

Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial

Check for updates

see commentary on page 25

Aditi Sinha[1], Mamta Puraswani[1], Mani Kalaivani[2], Pragya Goyal[1], Pankaj Hari[1] and Arvind Bagga[1]

[1]Division of Nephrology, Department of Pediatrics, Indian Council of Medical Research Advanced Center for Research in Nephrology, India Institute of Medical Sciences, New Delhi, India; and [2]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

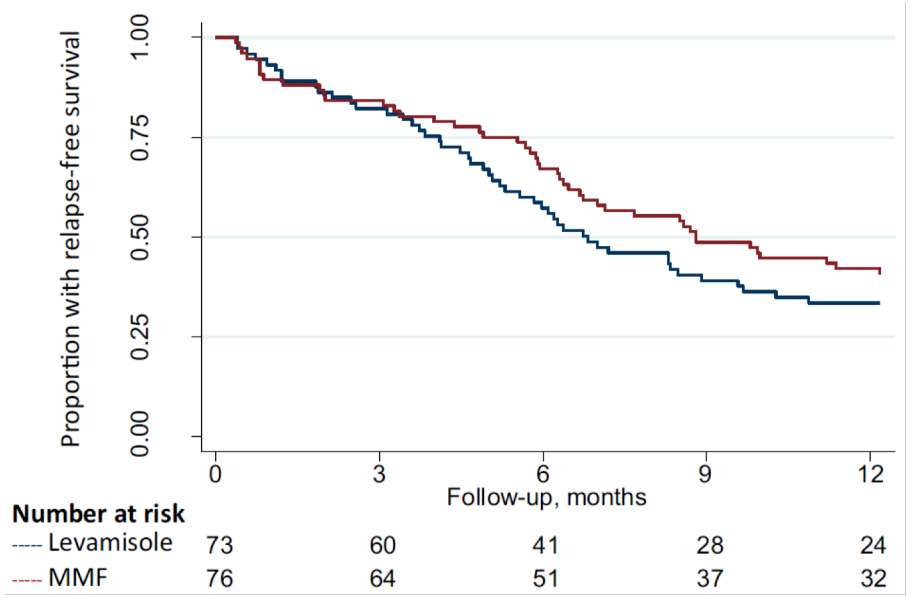
- **QOD levamisole 2.5 mg/Kg (n=73)**

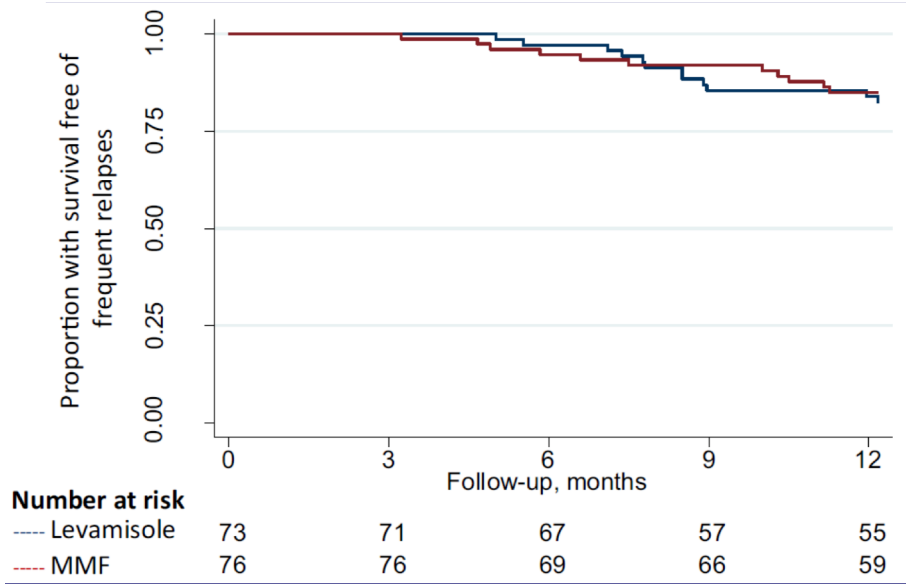
  vs.

  BID MMF 750-1000 mg/m²/d (n=76)

- Stop PDN after 2-3 months

- **MMF was NOT superior to levamisole** in:
  - frequency of relapses
  - likelihood of sustained remission
  - corticosteroid sparing



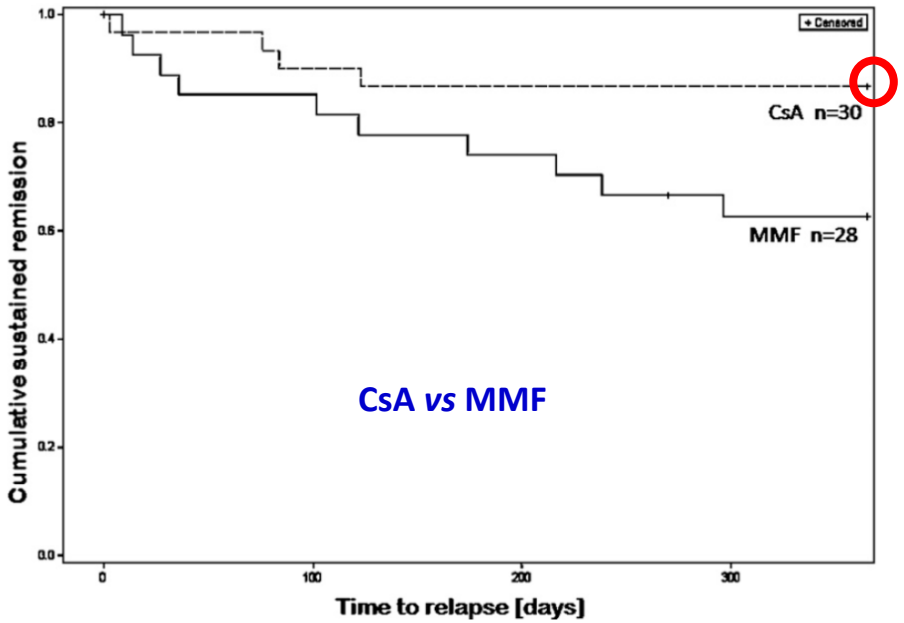


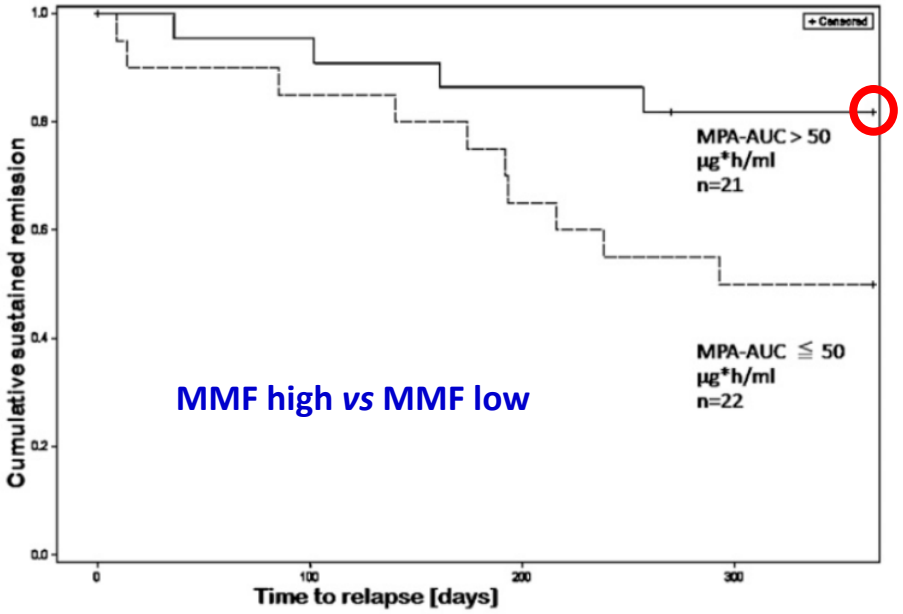
Kidney Int 2018

MMF vs CsA

Mycophenolate Mofetil versus Cyclosporin A in Children with Frequently Relapsing Nephrotic Syndrome

Jutta Gellermann,* Lutz Weber,† Lars Pape,‡ Burkhard Tönshoff,§ Peter Hoyer,‖ and Uwe Querfeld,* for the Gesellschaft für Pädiatrische Nephrologie (GPN)





Gellermann et al, JASN 2013

MMF AUC/C_{12}

Nephrol Dial Transplant (2008) 23: 3514–3520
doi: 10.1093/ndt/gfn360
Advance Access publication 27 June 2008

NDT Nephrology Dialysis Transplantation

Original Article

Association between mycophenolic acid 12-h trough levels and clinical endpoints in patients with autoimmune disease on mycophenolate mofetil

Irmgard Neumann[1], Heinz Fuhrmann[1], I-Fei Fang[2], Adelheid Jaeger[1], Peter Bayer[2] and Josef Kovarik[1]

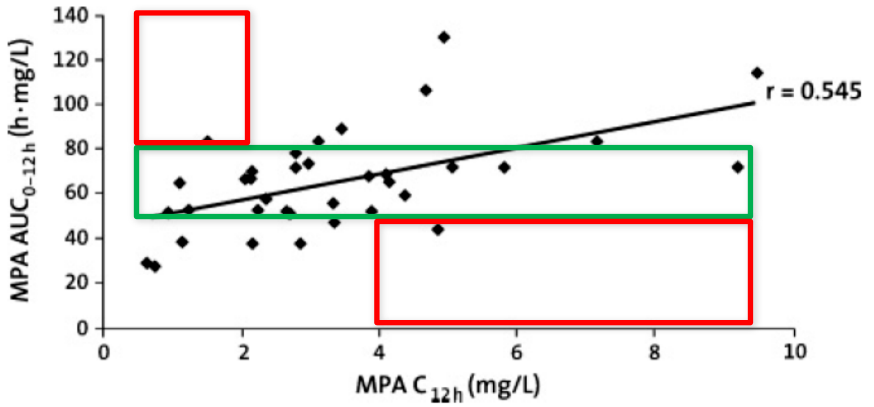
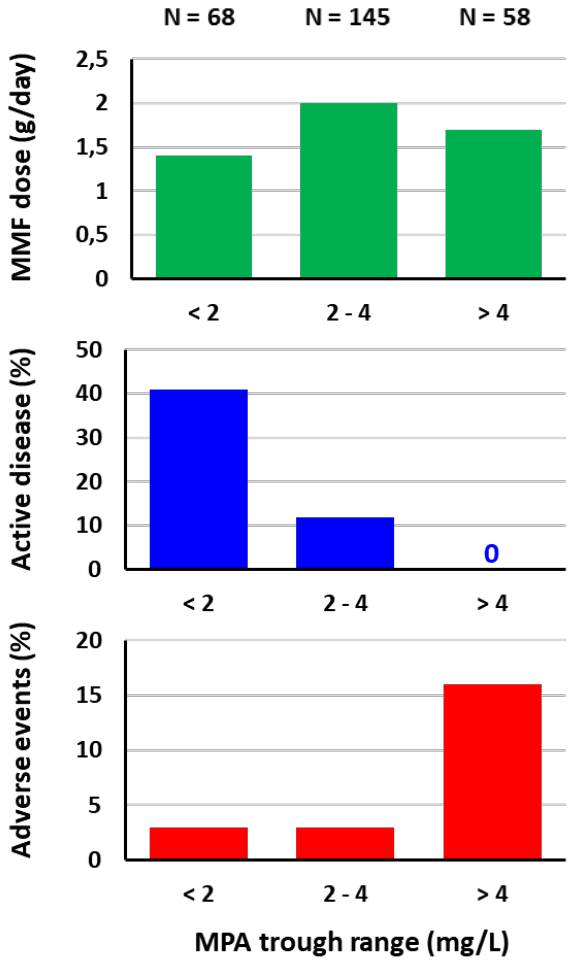


Fig. 1. Relationship between mycophenolic acid (MPA) plasma concentration at 12 h ($C_{12\,h}$) and $AUC_{0–12\,h}$ for MMF following an oral dose of 1 g in patients with autoimmune disease.



Adapted from Neumann et al, NDT 2008

MMF for SSNS

If a patient is not well controlled with MMF:

- If through levels are < 3 mg/ml, increase the dose
- If through levels are > 3 mg/ml, measure AUC and increase the dose if the AUC is low
- If no access to MPA levels and no apparent side effects, prudently increase the dose

MMF for SSNS

If a patient is not well controlled with MMF:

- If through levels are < 3 mg/ml, increase the dose
- If through levels are > 3 mg/ml, measure AUC and increase the dose if the AUC is low
- If no access to MPA levels and no apparent side effects, prudently increase the dose

If a patient is well controlled with MMF but has high through levels:

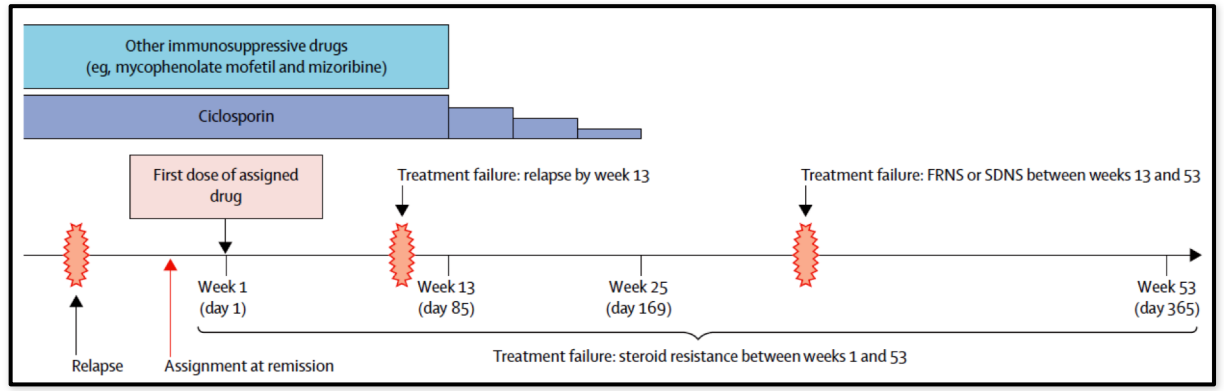
- If no apparent side effects, monitor
- If through levels are persistently high, measure AUC

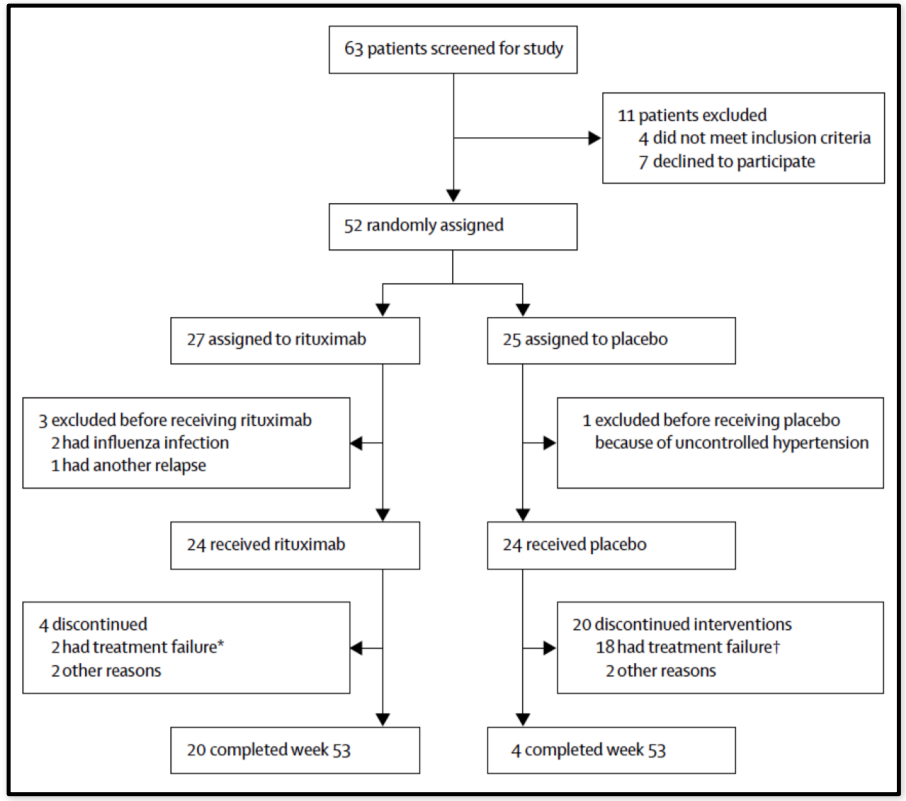
Rituximab for INS

Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial

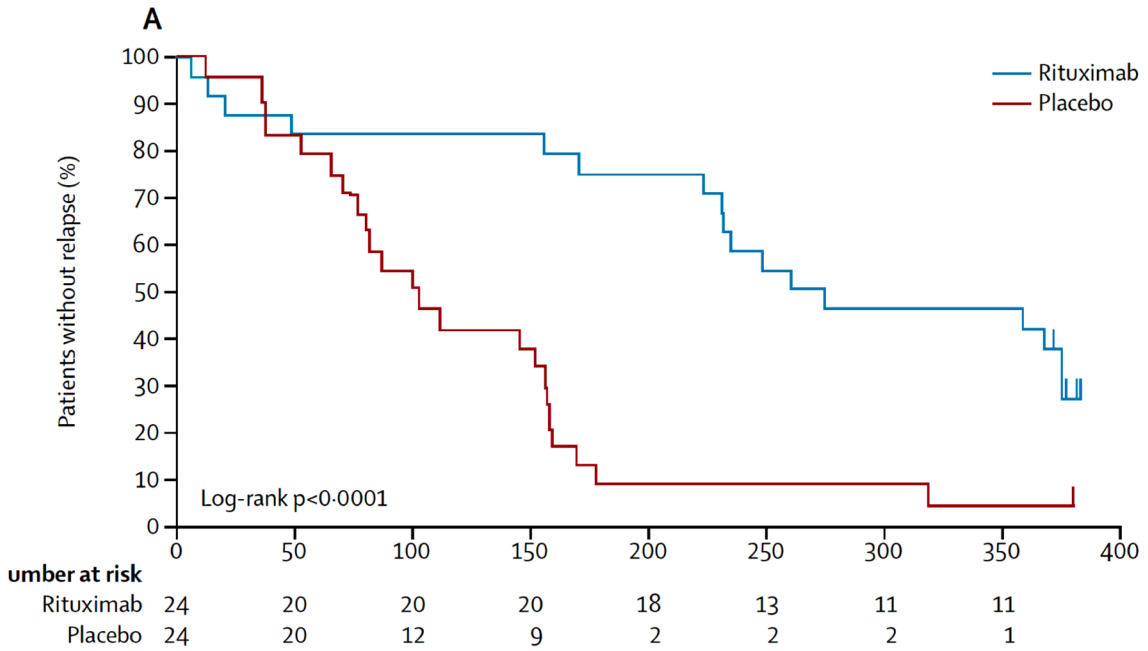
Kazumoto Iijima, Mayumi Sako, Kandai Nozu, Rintaro Mori, Nao Tuchida, Koichi Kamei, Kenichiro Miura, Kunihiko Aya, Koichi Nakanishi, Yoshiyuki Ohtomo, Shori Takahashi, Ryojiro Tanaka, Hiroshi Kaito, Hidefumi Nakamura, Kenji Ishikura, Shuichi Ito, Yasuo Ohashi, on behalf of the Rituximab for Childhood-onset Refractory Nephrotic Syndrome (RCRNS) Study Group

Lancet 2014





FRNS/SDNS on other steroid-sparing IS therapies



RTX vs Tacrolimus for SDNS: RCT

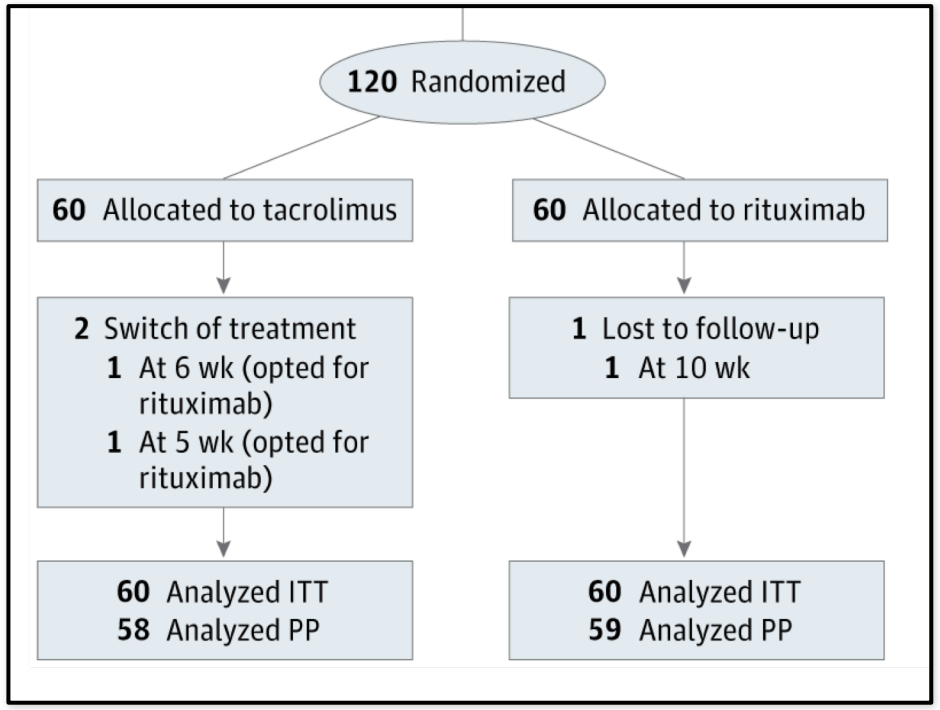
JAMA Pediatrics | Original Investigation 2018

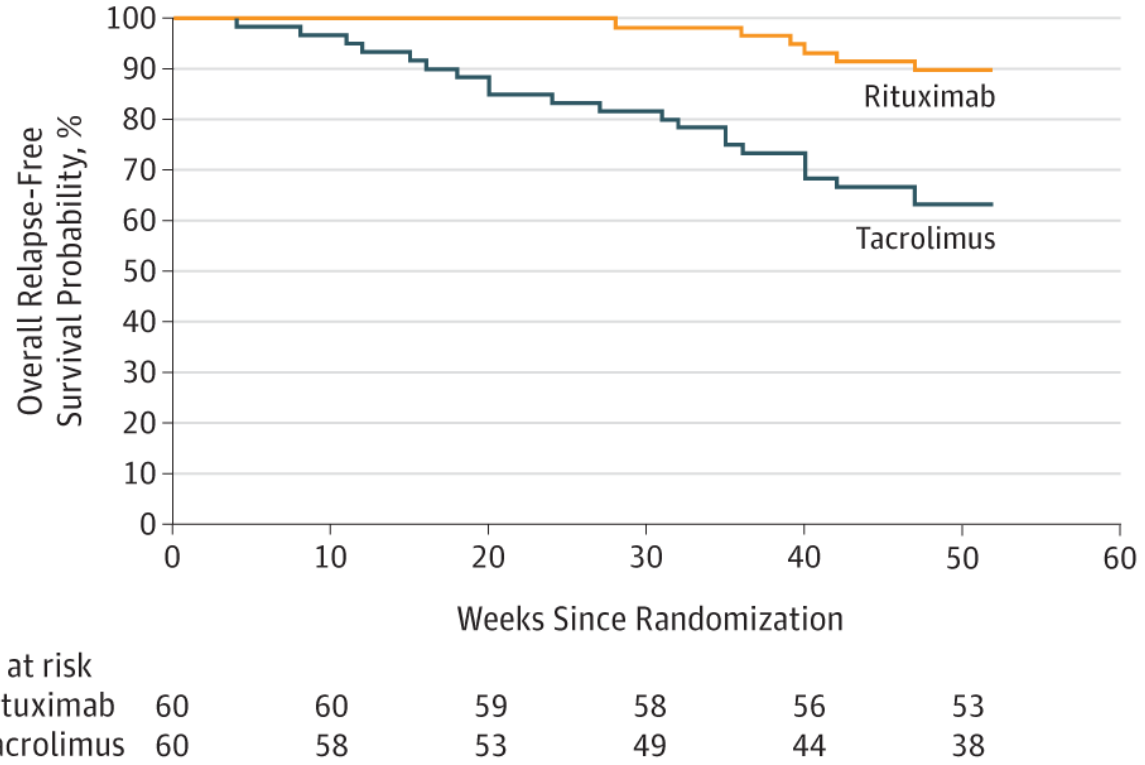
Efficacy of Rituximab vs Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome

A Randomized Clinical Trial

Biswanath Basu, MD; Anja Sander, PhD; Birendranath Roy, MD; Stella Preussler, MSc; Shilpita Barua, MD; T. K. S. Mahapatra, MD; Franz Schaefer, MD

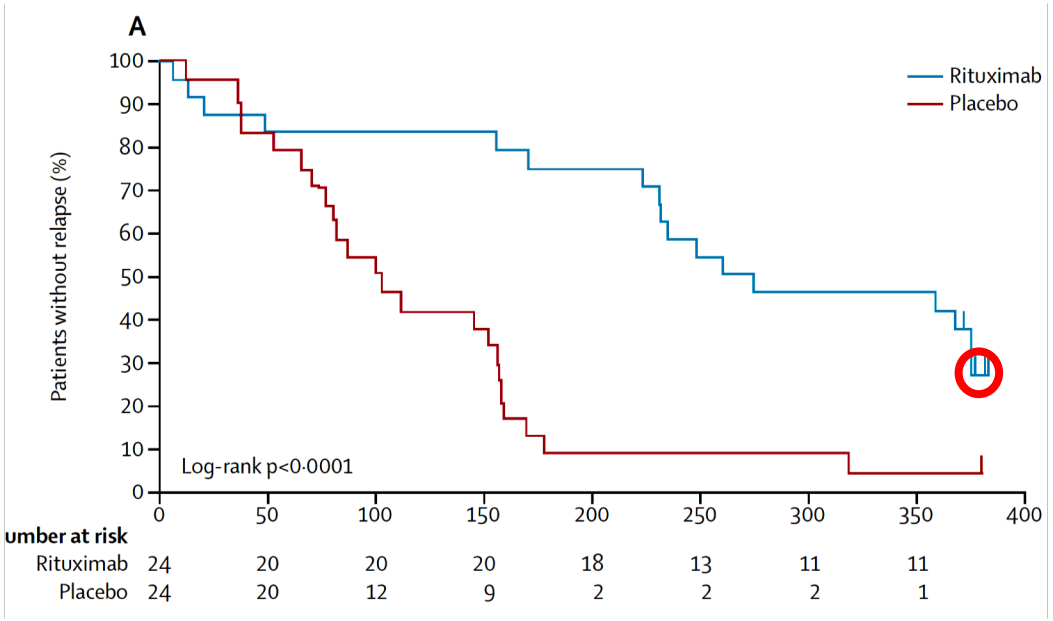
SDNS: NO previous steroid sparing therapies



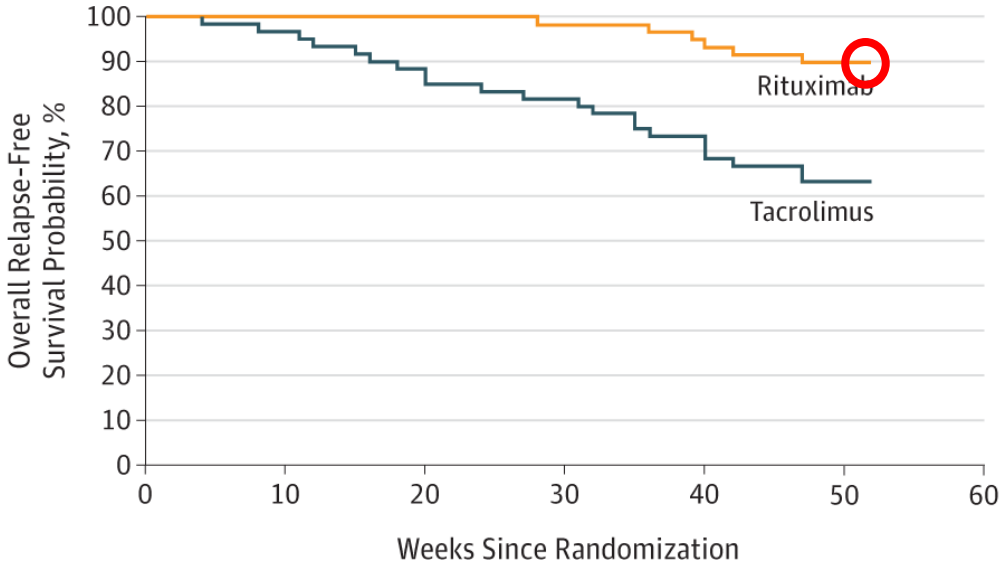


Rituximab for INS

FRNS/SDNS on other steroid-sparing IS therapies



SDNS: NO previous steroid sparing therapies



Bambino Gesù
OSPEDALE PEDIATRICO

Iijima et al, Lancet 2014

Basu B, JAMA Pediatrics 2018

Retrospective analysis of 511 children treated with RTX

Both the rituximab dose and maintenance immunosuppression in steroid-dependent/ frequently-relapsing nephrotic syndrome have important effects on outcomes

Eugene Yu-hin Chan[1,2,3], Hazel Webb[1], Ellen Yu[4], Gian Marco Ghiggeri[5], Markus J. Kemper[6], Alison Lap-tak Ma[2,3], Tomohiko Yamamura[7], Aditi Sinha[8], Arvind Bagga[8], Julien Hogan[9], Claire Dossier[9], Marina Vivarelli[10], Isaac Desheng Liu[11], Koichi Kamei[12], Kenji Ishikura[12,13], Priya Saini[14,15] and Kjell Tullus[1]

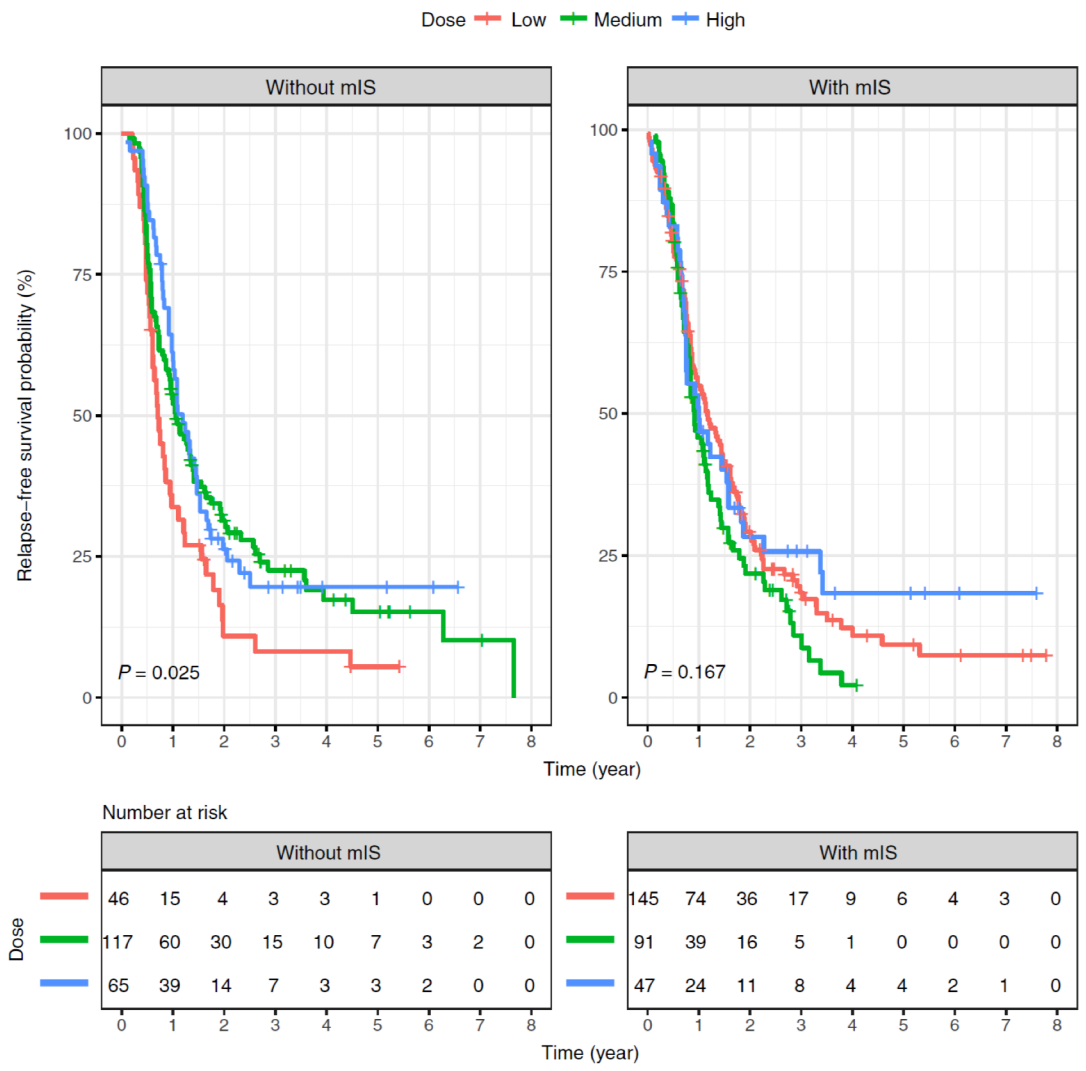
Dose of rituximab:

- Low dose: **375 mg/m² (n=191)**
- Medium dose: **750 mg/m² (n=208)**
- High dose: **1125-1500 mg/m² (n=112)**

Table 3 | Primary outcomes: relapse-free survival following rituximab therapy

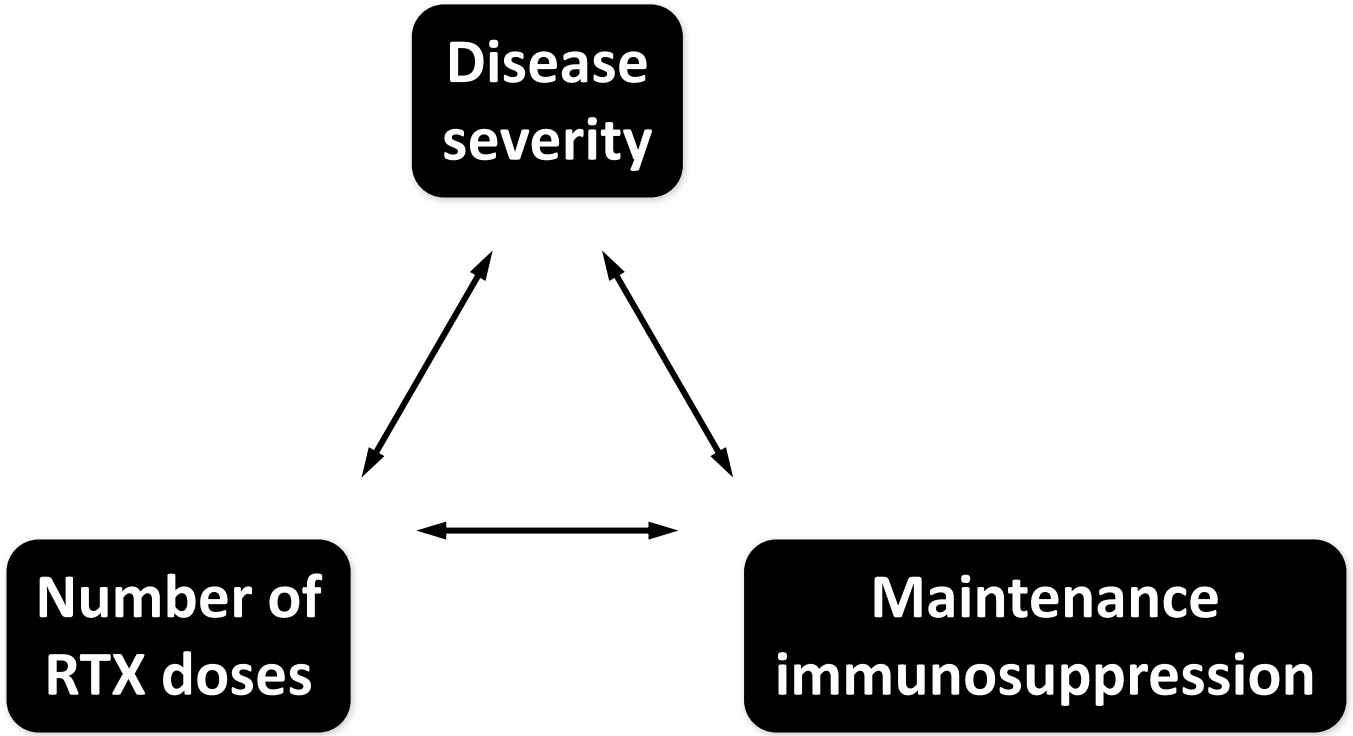
	Relapse-free time (mo)			
	Low dose	Medium dose	High dose	*P* value
All	11.8 (10.1–15.8)	11.9 (10.4–14.3)	13.0 (11.8–17.4)	0.36
Without mIS	8.5 (7.2–13.3)	12.7 (10.4–16.9)	14.3 (12.0–18.4)	0.03
With mIS	14.0 (11.0–18.1)	10.9 (10.0–14.2)	12.0 (9.0–22.0)	0.17

mIS, maintenance immunosuppression.
Values are medians (95% confidence intervals).



Kidney Int 2020

Rituximab efficacy in SSNS

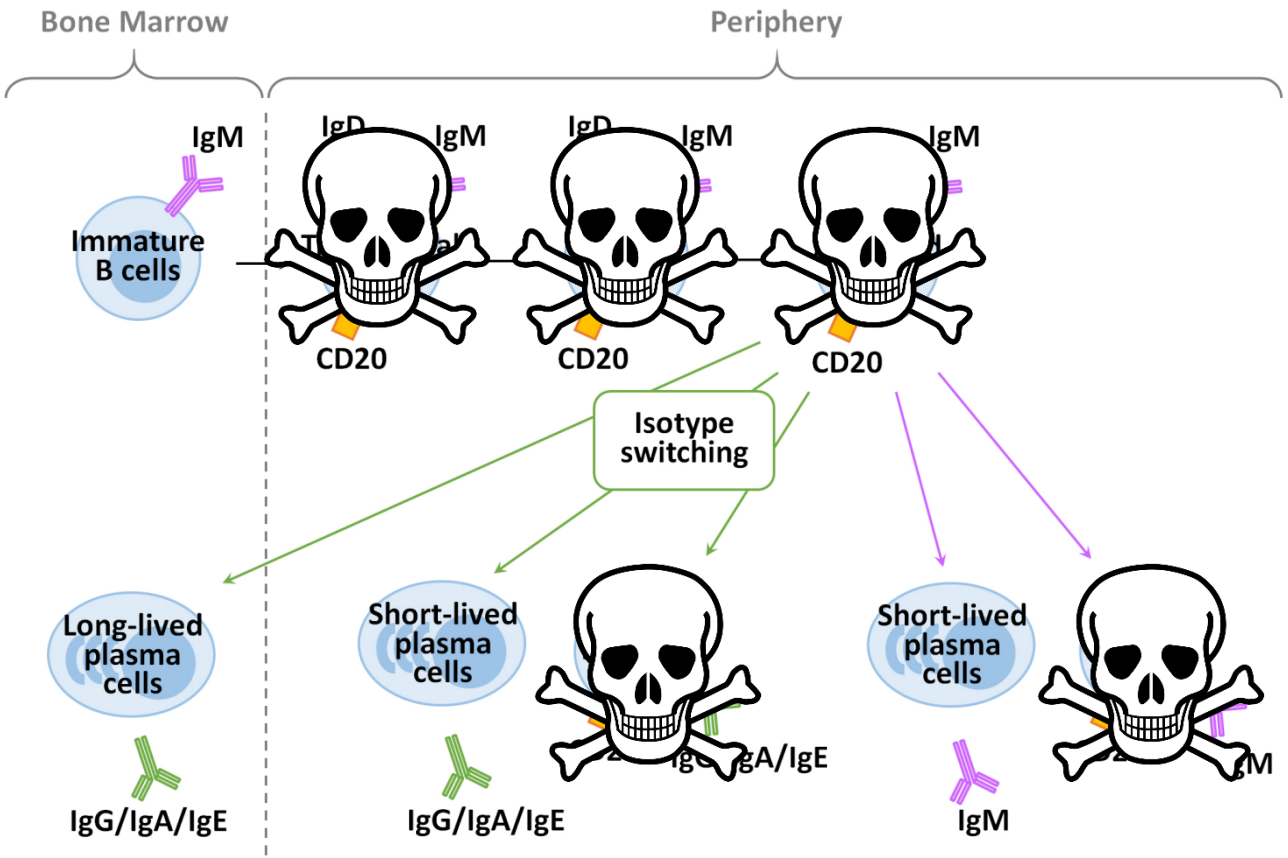


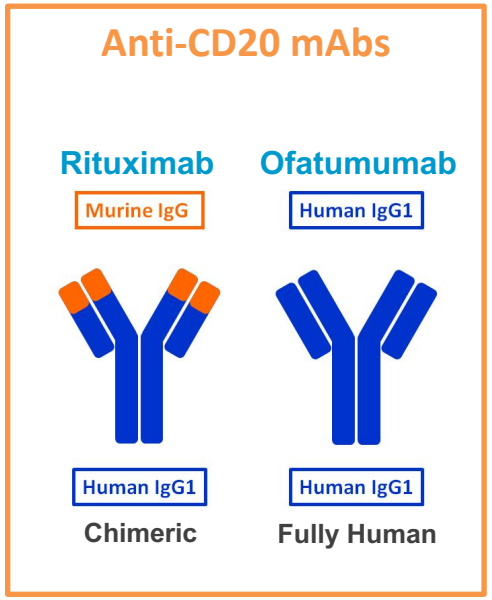
Rituximab for SSNS

Severity of INS	Estimated 1 year remission rate w/o IS therapy
FRNS	~ 50-70%
SDNS	~ 30-40%
Severe SDNS	<30%
SRNS	<15%

Maintain IS therapy
or
Start with 2 doses and
repeat every 6 months

Anti CD20 monoclonal antibosied for INS

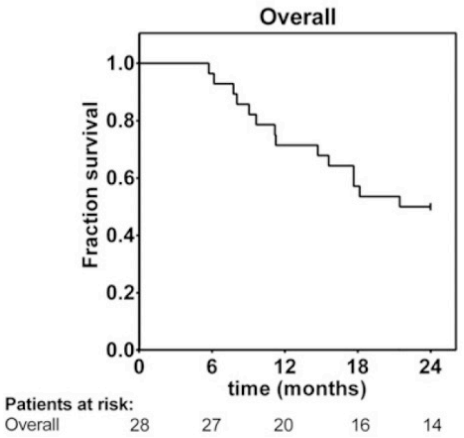


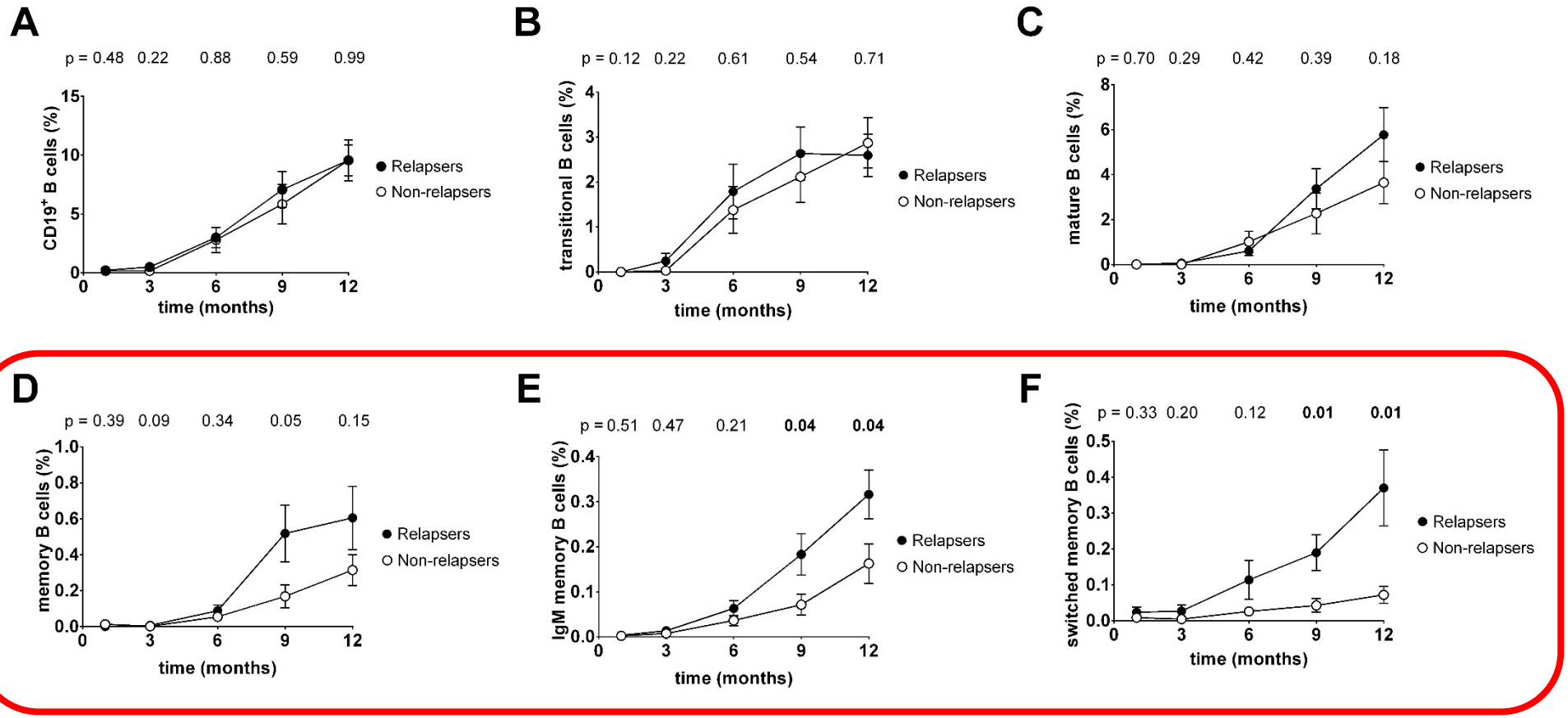


Bambino Gesù
OSPEDALE PEDIATRICO

Colucci et al, Ped Nephrol 2017

Different reconstitution of memory cells post-RTX in non-relapsers





Colucci et al, JASN 2016

Question 2

Rituximab causes persistent hypogammaglobinemia in:

1. <5% of patients
2. 5-10% of patients
3. 10-15% of patients
4. >15% of patients

Long-term adverse events in 26 children with INS treated with RTX

Prolonged Impairment of Immunological Memory After Anti-CD20 Treatment in Pediatric Idiopathic Nephrotic Syndrome

Manuela Colucci[1], Rita Carsetti[2], Jessica Serafinelli[3], Salvatore Rocca[4], Laura Massella[3], Antonio Gargiulo[3], Anna Lo Russo[5], Claudia Capponi[2], Nicola Cotugno[4], Ottavia Porzio[6], Andrea Onetti Muda[6], Paolo Palma[4], Francesco Emma[1,3] and Marina Vivarelli[1,3]*

5 years from the first infusion

>2 years from the last infusion

Frontiers Immunol 2019

Parameter	N (%)
Treatment	
One infusion	15 (58)
Multiple infusions	11 (42)
B-cell reappearance < 12 months	26 (100)
Serious adverse events	
Infections (pneumonia, EBV, HZV, HHV6, encephalitis, otitis)	9 (35)
Lymphatic disorders (lymphadenopathy, leukopenia)	2 (8)
Thrombocytopenia	1 (4)
Allergic episodes	2 (8)
Moderate hypogammaglobulinemia (IgG<700 mg/dl)	7 (27)
Severe hypogammaglobulinemia (IgG<150 mg/dl) requiring Ig supplementation	3 (12)

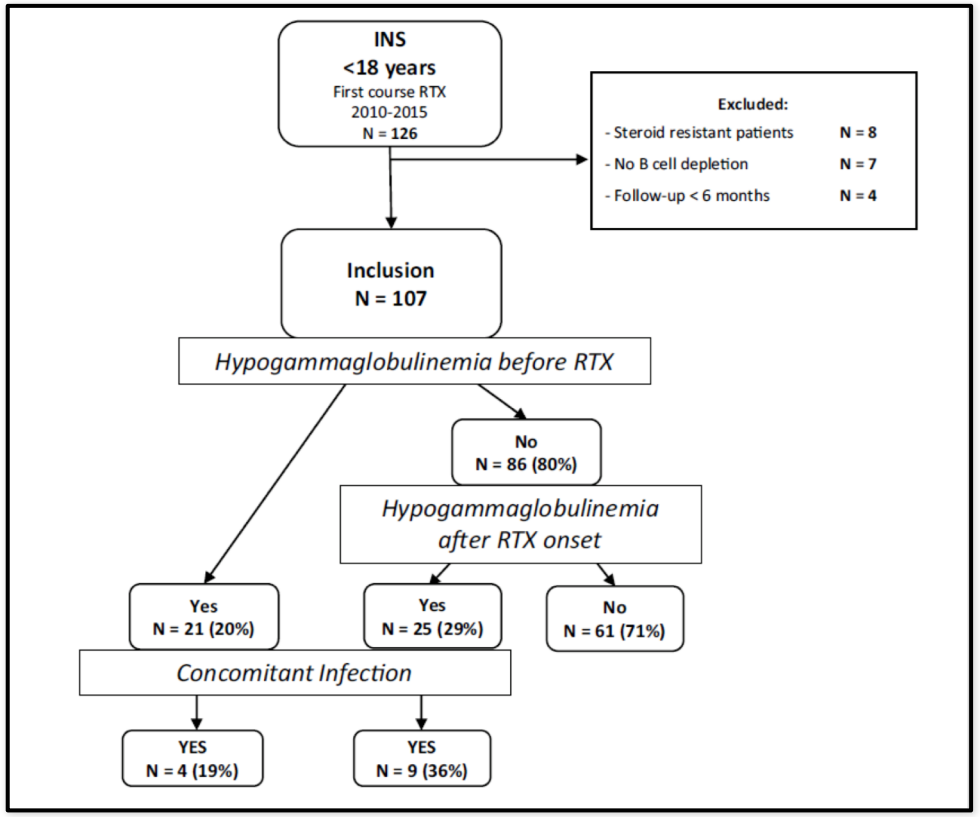
Long-term adverse events in 26 children with INS treated with RTX

Pediatric Nephrology (2020) 35:455–462
https://doi.org/10.1007/s00467-019-04398-1

ORIGINAL ARTICLE

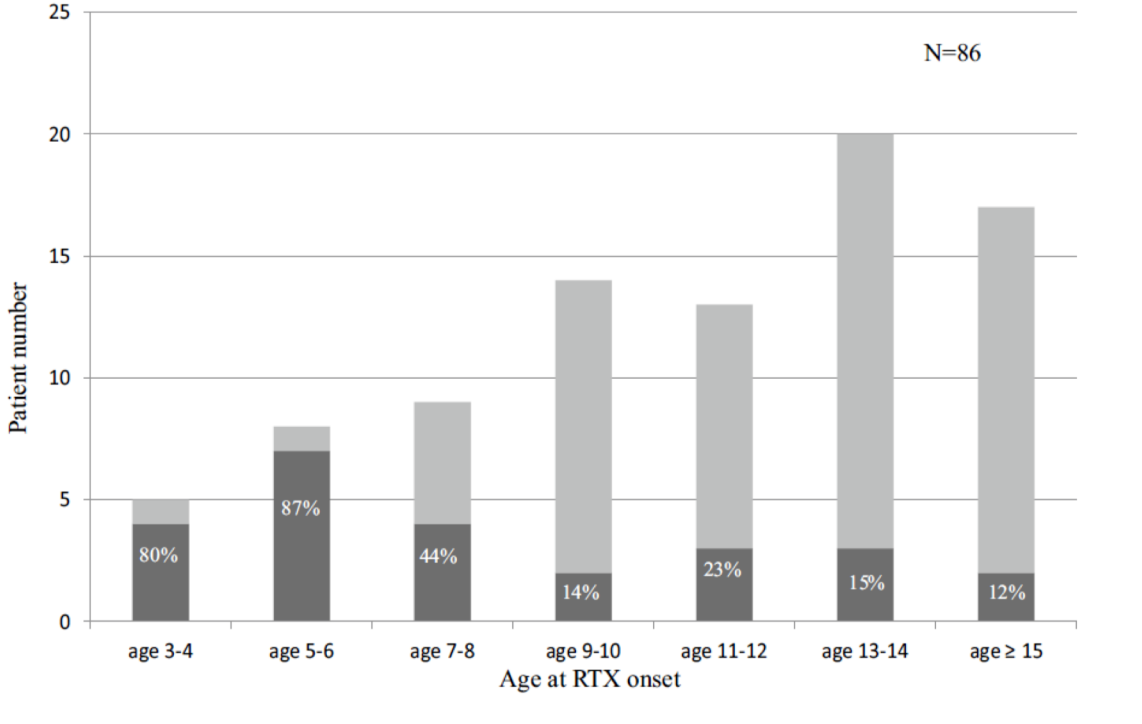
Immunoglobulin serum levels in rituximab-treated patients with steroid-dependent nephrotic syndrome

Cyrielle Parmentier[1,2,3] · Jean-Daniel Delbet[1,3] · Stéphane Decramer[4] · Olivia Boyer[5] · Julien Hogan[6] · Tim Ulinski[1,2,3]

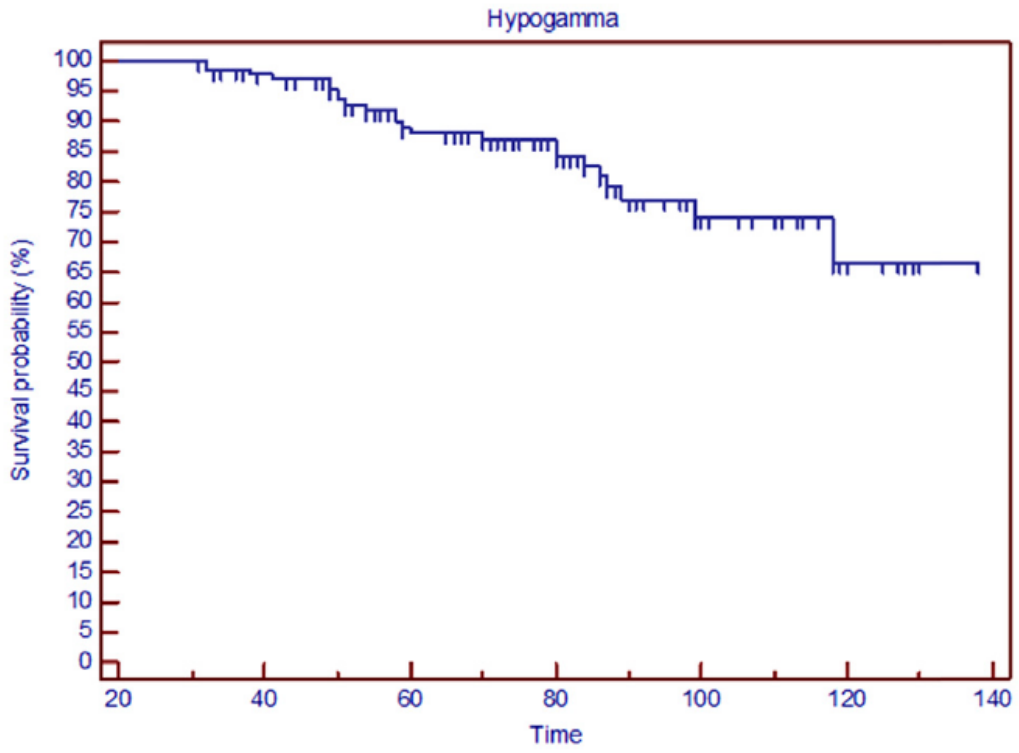


Younger age are at higher risk

Not dose dependent

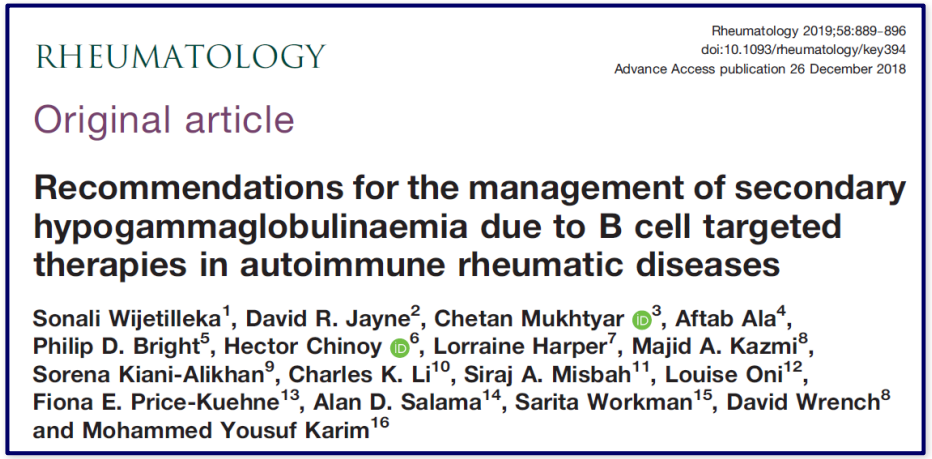


Post-RTX hypogammaglobulinemia in 134 adults patients with rheumatoid arthritis



Boleto et al, Sem Arthr Rheumat 2018

Hypogammaglobulinemia post-RTX



RHEUMATOLOGY

Rheumatology 2019;58:889–896
doi:10.1093/rheumatology/key394
Advance Access publication 26 December 2018

Original article

Recommendations for the management of secondary hypogammaglobulinaemia due to B cell targeted therapies in autoimmune rheumatic diseases

Sonali Wijetilleka[1], David R. Jayne[2], Chetan Mukhtyar[3], Aftab Ala[4], Philip D. Bright[5], Hector Chinoy[6], Lorraine Harper[7], Majid A. Kazmi[8], Sorena Kiani-Alikhan[9], Charles K. Li[10], Siraj A. Misbah[11], Louise Oni[12], Fiona E. Price-Kuehne[13], Alan D. Salama[14], Sarita Workman[15], David Wrench[8] and Mohammed Yousuf Karim[16]

- Inform about the possibility and implications of developing hypogammaglobulinaemia
- Measure Ig levels before RTX and every 6-12 months thereafter
- A low IgG level is not an absolute contra-indication to RTX
- Symptomatic hypogammaglobulinaemia:
  no available evidence comparing antibiotic prophylaxis with immunoglobulin replacement therapy
- Non symptomatic severe hypogammaglobulinaemia (e.g. < 2g/l):
  no evidence whether to treat, and how to treat

In conclusion

- The initial PDN protocol does has limited impact on the outcome of SSNS
  PDN tapering schedules have little rationale
- CNI are efficient in severe forms of SSNS
  (avoid prolonged treatment and high drug levels)
- Levamisole is cheap and is efficient for the treatment of mild forms of SSNS
  (monitor ANCA)
- MMF is very effective, but patients may need high doses
  (side effects usually parallel MPA levels)
- The efficacy of RTX depends on the severity of NS and treatment schedules
  Protocols should be adapted to the severity of the disease
  Hypogammaglobinemia is a growing concern

Thank you

francesco.emma@opbg.net

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IPNA Clinical Practice Webinars

Date: 06 February 2020

Speaker: Justine Bacchetta (Lyon, France)

Topic: Cinacalcet use in paediatric dialysis: a position statement from the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders Working Group of the ERA-EDTA.

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 11 Feburary 2020

Speaker: Beata Lipska-Zietkiewicz (Gdansk, Poland)

Topic: Genetics: Basic Concepts and Testing

ERKNet Advanced Webinars on Rare Kidney Disorders

Date: 25 February 2020

Speaker: John Sayer (Newcastle, UK)

Topic: Joubert syndrome – molecular genetics and therapies

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