

Treatment of Steroid Dependent and Frequently Relapsing NS



Kjell Tullus

Consultant Paediatric Nephrologist

Different clinical forms

- Simple course
 - A number of relapses over the coming years and then growing out of the problem
- Steroid resistant
 - Not responding within 1 month to steroids
- Steroid dependent
 - Relapsing when reducing steroid dose
- Frequently relapsing
 - Several relapses during one year

Why start second line treatment?



- To avoid steroid toxicity
- The frequency of relapses but also the time to response will thus matter

Tom 3.5 years old

- Onset NS at three years of age.
- During the first six months he had three relapses attributed to URTIs
- No major oedema
- Responded to steroid treatment within a week.
- What to do next?

Lower steroid dose during relapses

- We now routinely use 1mg/kg of prednisolone to treat a relapse
- Fifty children with 87 relapses
- 70% responded within one week to the low dose.
- They had significantly lower rate of side-effects

Arvind 6 years old

- Onset of NS at 4 years of age
- First year two relapses
- Second year four relapses
- Responds well to treatment but it can take up to 2-3-4 weeks to respond
- What to do next?

Treatment of steroid dependent/ frequently relapsing



- Levamisole

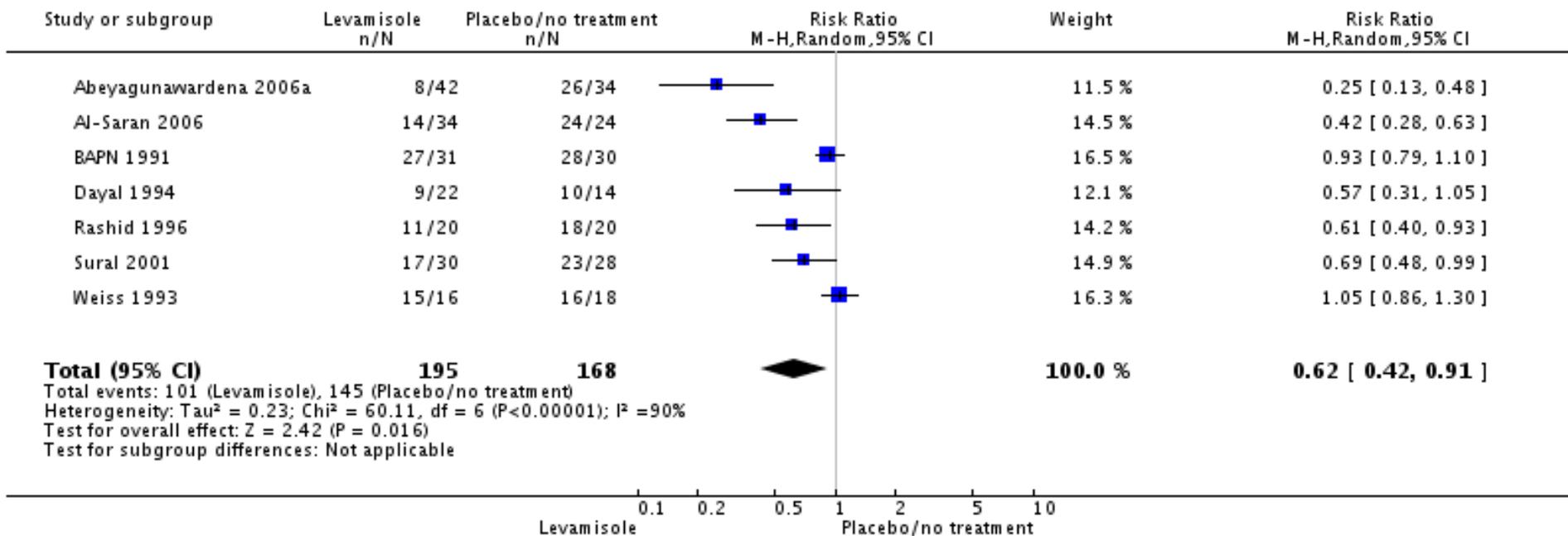
Levamisole



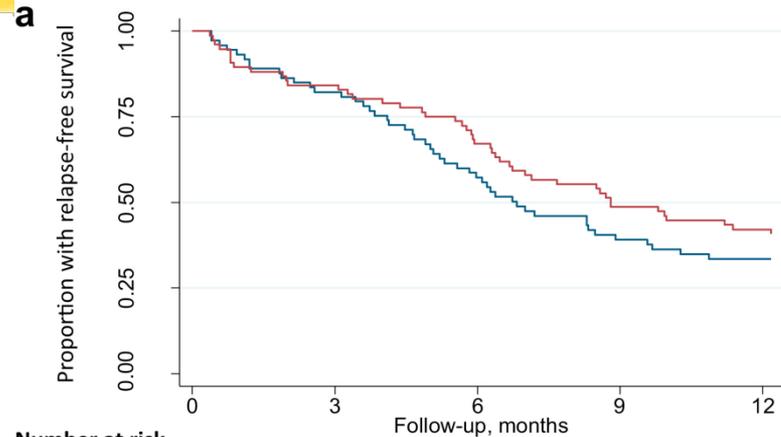
- Antihelmintic drug
- Proven effect in studies in the UK
- Many countries do not use it

Levamisole vs placebo or no treatment

Review: Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children
 Comparison: 12 Levamisole versus steroids or placebo or both, or no treatment
 Outcome: 2 Relapse at 6 to 12 months

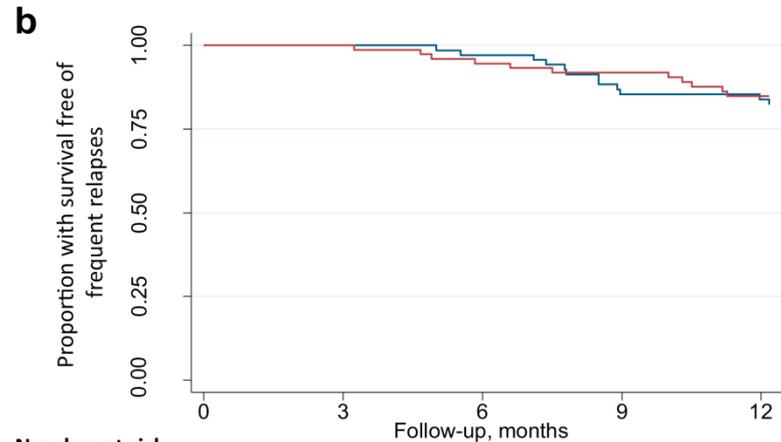


Levamisole compared to MMF



Number at risk

Follow-up, months	Levamisole	MMF
0	73	76
3	60	64
6	41	51
9	28	37
12	24	32



Number at risk

Follow-up, months	Levamisole	MMF
0	73	76
3	71	76
6	67	69
9	57	66
12	55	59

Treatment of steroid dependent/ frequently relapsing



- Levamisole
- Low dose steroids every other day

Low dose every other day steroids



- No good data
- Still used a lot and recommended by KDIGO

Treatment of steroid dependent/ frequently relapsing



- Levamisole
- Low dose steroids every other day
- Steroids during infection

Steroids during infection

- 36 children with SDNS treated with 0.5mg/kg of prednisolone
- Half of them were given daily prednisolone for five days during URTI
- Two year follow-up
 - 40 relapses (mean 2.2/year) in treatment group
 - 99 relapses (mean 5.5/year) in placebo group

Tanzeelah 5 years old

- Onset NS at the age of four years
- Quite a severe oedema during the first episode
- Responded to steroids after 3.5 weeks
- Weaned slower than we do regularly
- Relapsed while still on 10mg Prednisolone every other day
- What to do next?

Treatment of steroid dependent/ frequently relapsing



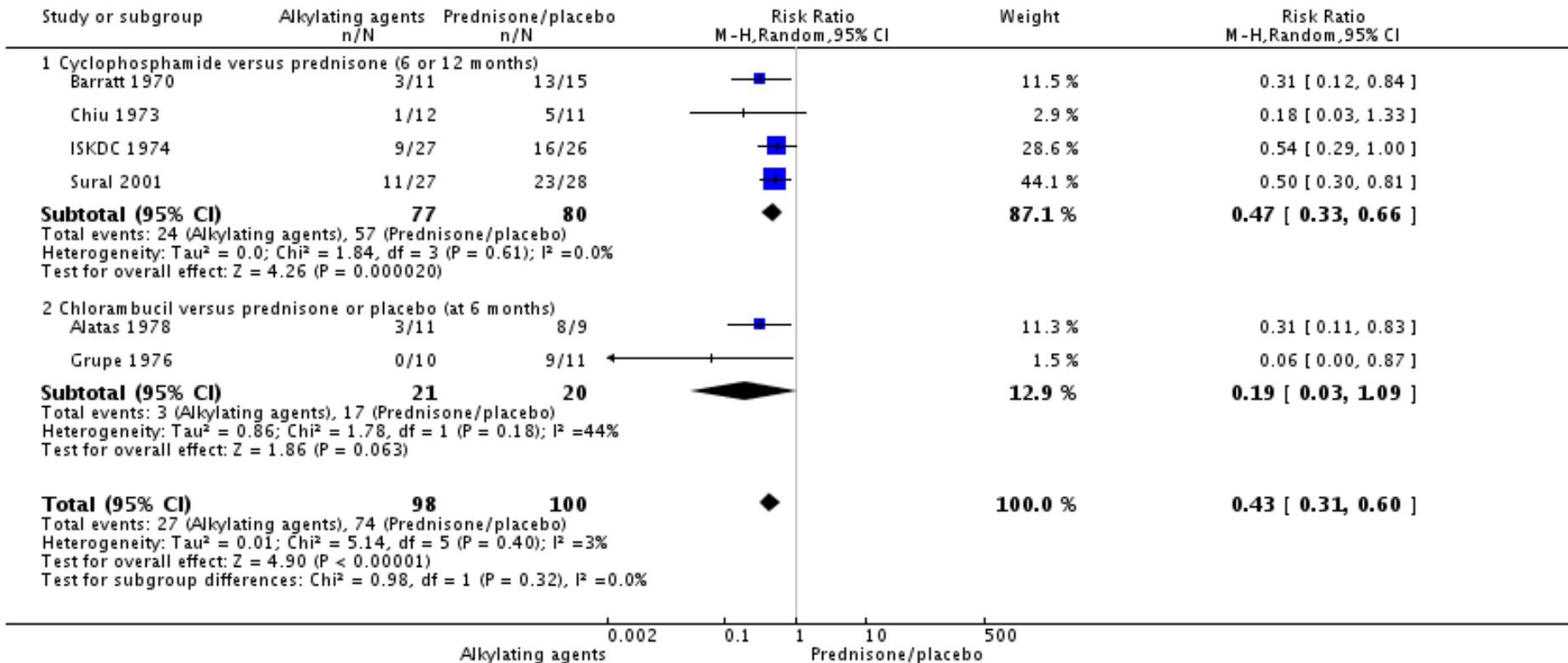
- Levamisole
- Low dose steroids every other day
- Steroids during infection
- Cyclophosphamide

Cyclophosphamide

- Two month course of oral 3mg/kg/day
- Monitor FBC
- Works well in a third of patients
- Does not help another third of the kids

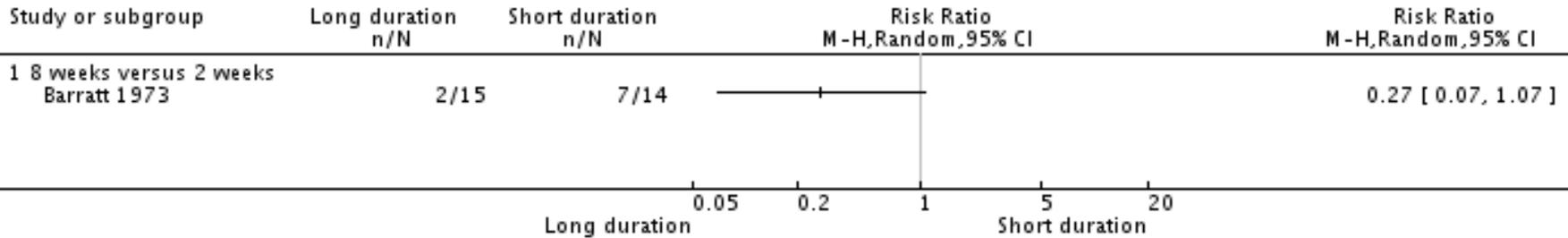
Cyclophosphamide

Review: Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children
 Comparison: 1 Alkylating agents versus steroids or placebo or both
 Outcome: 1 Relapse at 6 to 12 months



Length of treatment

Review: Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children
Comparison: 2 Cyclophosphamide duration
Outcome: 1 Relapse at 6 months



Cyclophosphamide

Side-effects



- Reduction in neutrophils
- Severe infection
- Hair loss
- Infertility
- Increased risk of malignancies

Tanzeelah now 7 years old

- Tanzeelah had cyclophosphamide 1.5 years ago.
- Been free of relapses more than one year
- Parents very pleased
- But now had one relapse
- What to do next?

Tanzeelah now 7 years old

- Nothing except treating the relapse

Tanzeelah now 8 years old

- Has had three relapses over the last 6 month
- What to do next?

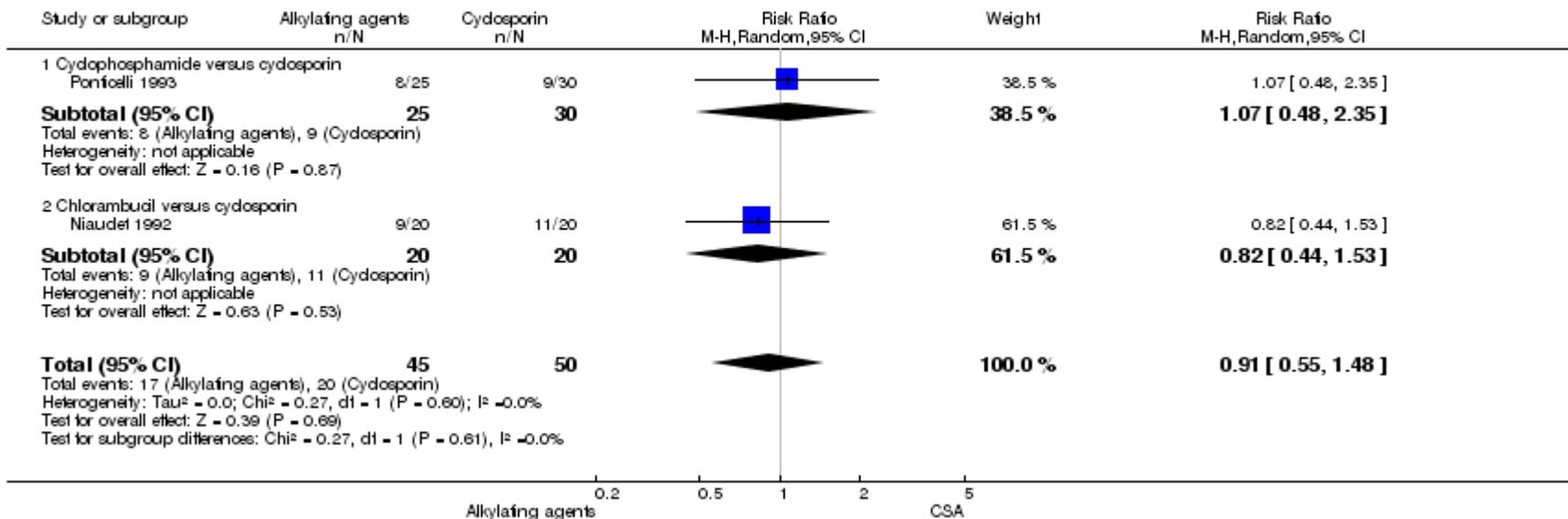
Treatment of steroid dependent/ frequently relapsing



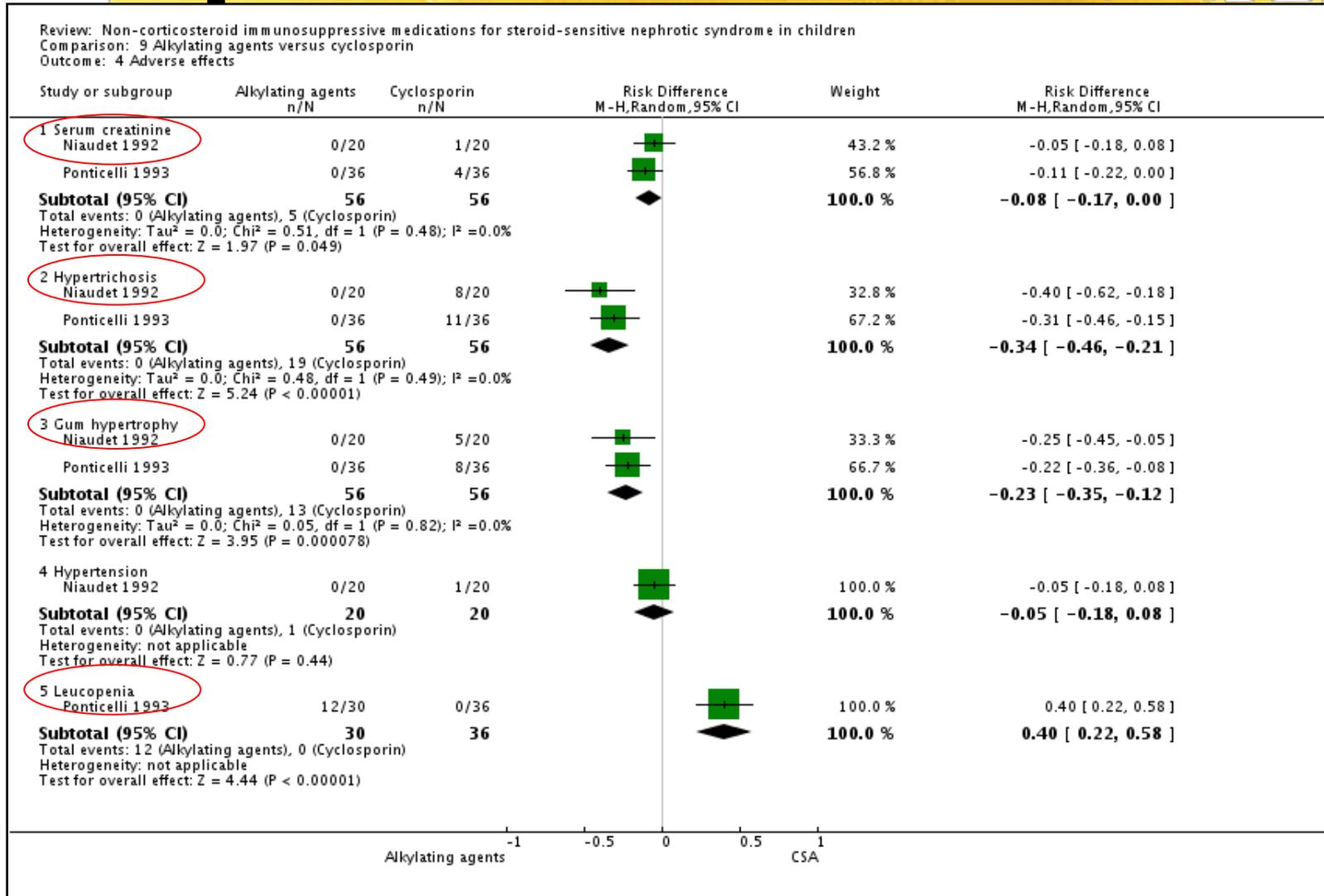
- Levamisole
- Low dose steroids every other day
- Steroids during infection
- Cyclophosphamide
- Cyclosporine

Cyclosporine vs alkylating agent

Review: Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children
 Comparison: 9 Alkylating agents versus cyclosporin
 Outcome: 1 Relapse at end of therapy (6 to 9 months)



Cyclosporine vs cyclophosphamide side-effects



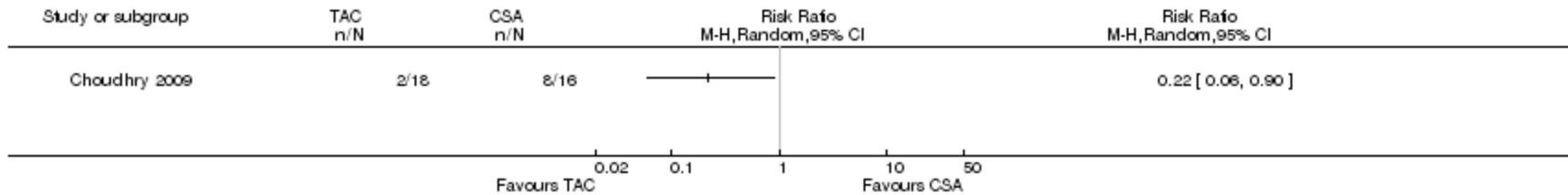
Treatment of steroid dependent/ frequently relapsing



- Levamisole
- Low dose steroids every other day
- Steroids during infection
- Cyclophosphamide
- Cyclosporine
- Tacrolimus

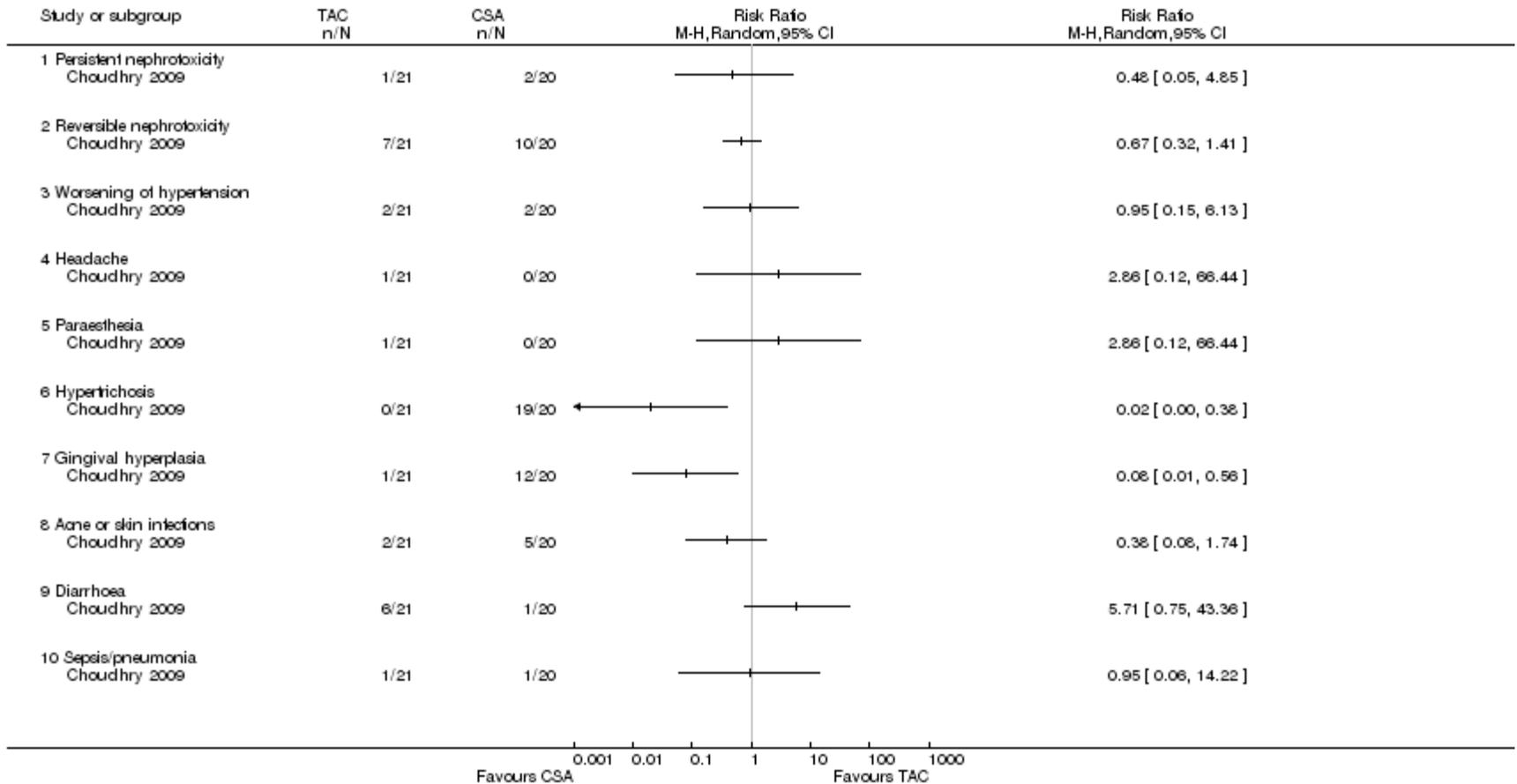
Tacrolimus vs cyclosporine

Review: Interventions for idiopathic steroid-resistant nephrotic syndrome in children
Comparison: 3 Tacrolimus versus cyclosporin
Outcome: 3 Relapse following complete or partial remission



Side effects

Review: Interventions for idiopathic steroid-resistant nephrotic syndrome in children
 Comparison: 3 Tacrolimus versus cyclosporin
 Outcome: 7 Adverse events



Tanzeelah now 11 years old

- Tacrolimus worked well for three years. Only infrequent relapses.
- What to do next?

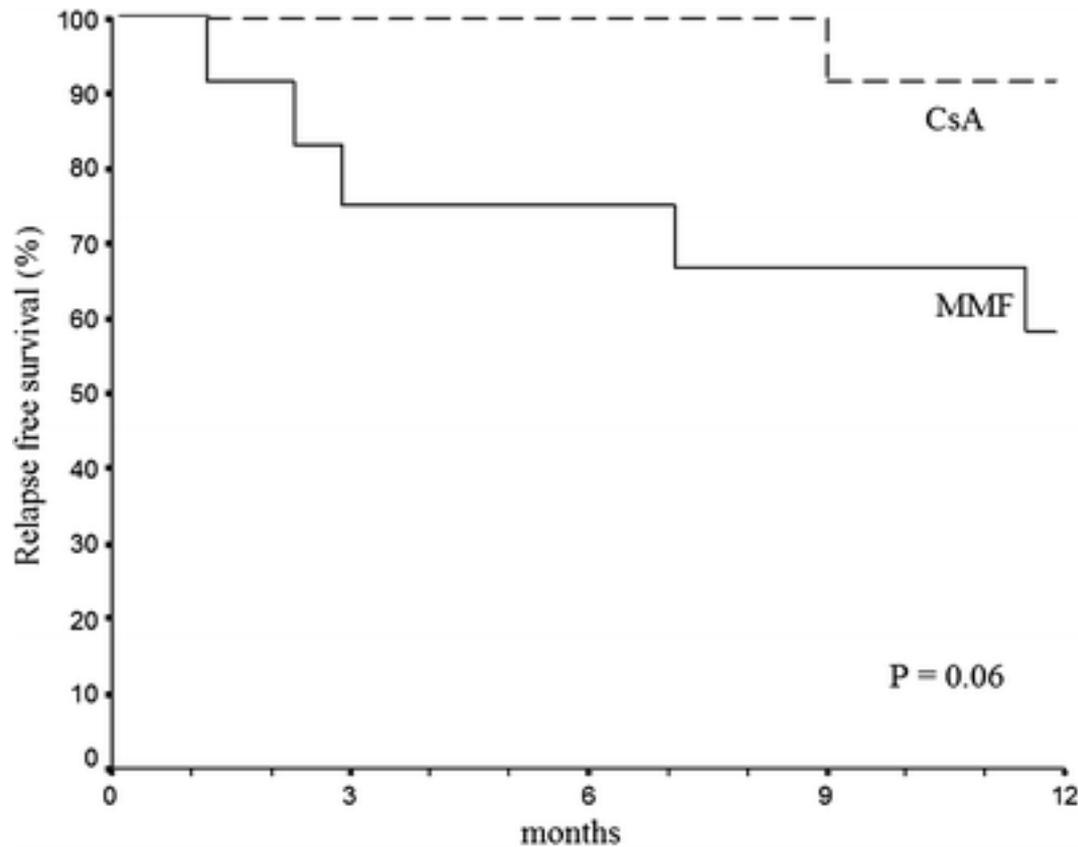
Treatment of steroid dependent/ frequently relapsing



- Levamisole
- Low dose steroids every other day
- Steroids during infection
- Cyclophosphamide
- Cyclosporine
- Tacrolimus
- **Mycophenolate**

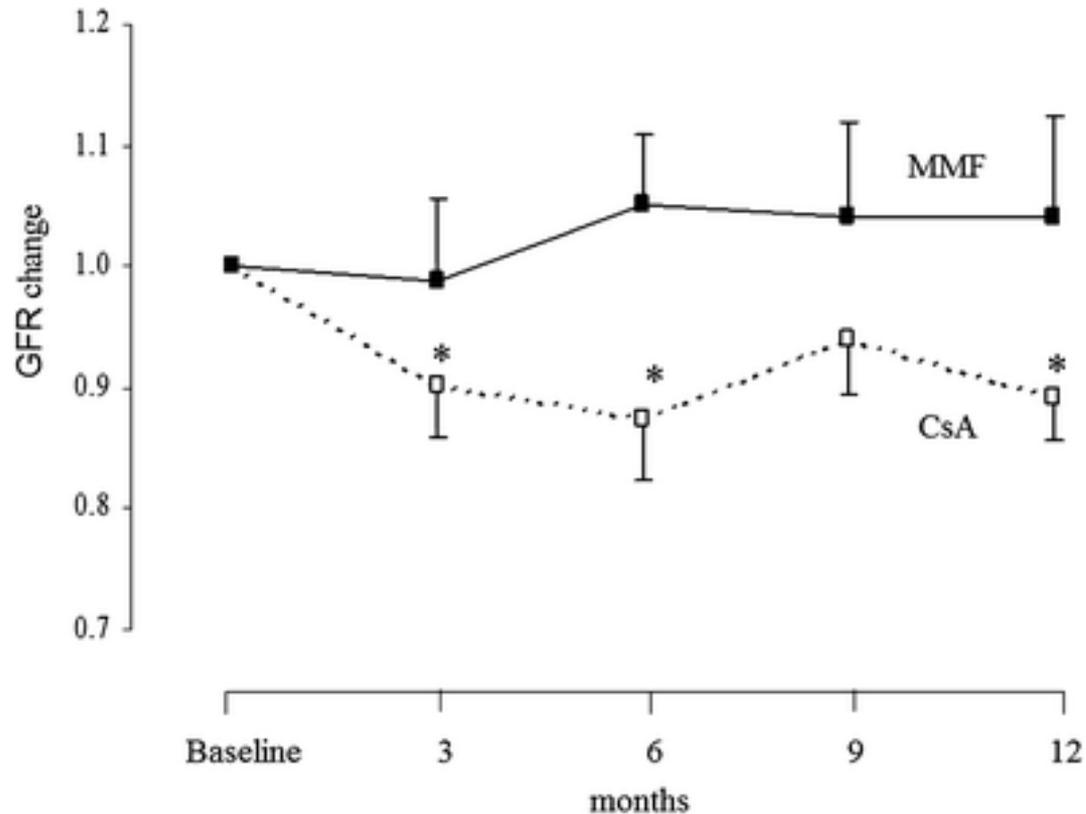
FRNS

12 children treated with MMF and 12 with CsA



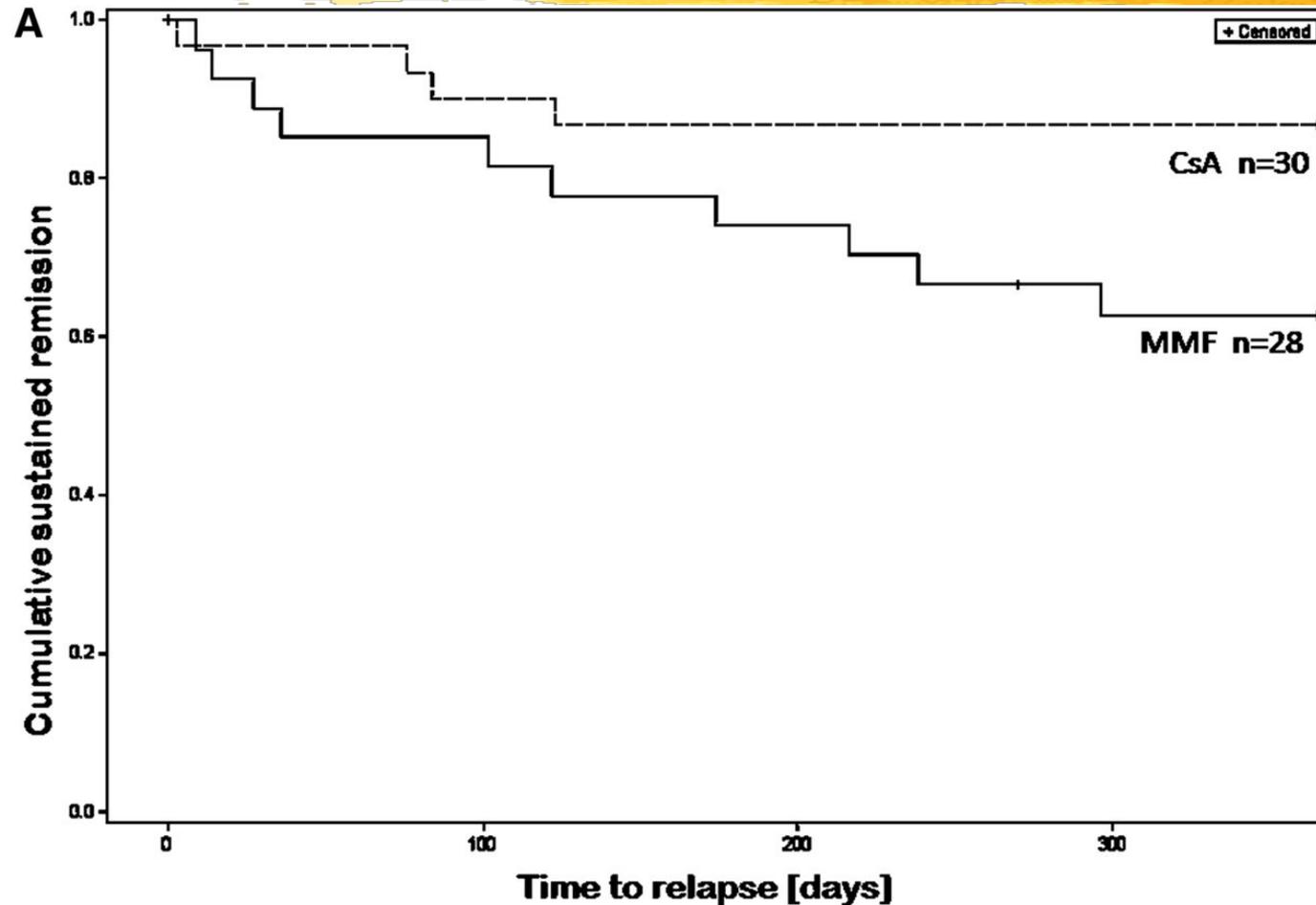
FRNS

12 children treated with MMF and 12 with CsA



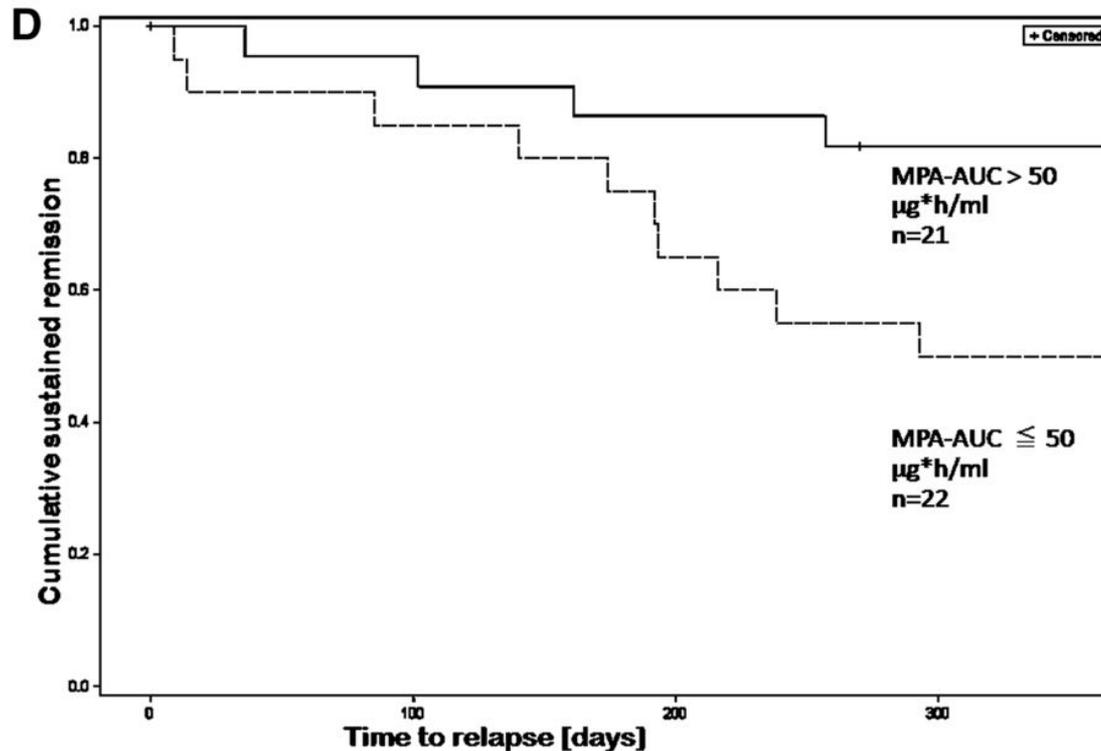
Dorresteijn et al Ped Nephrol 2008

Efficacy of CsA and MMF in preventing relapses in FR-SSNS patients.



D

Pharmacokinetics of MPA and efficacy.



MMF side effects



- Relatively mild
- Diarrhoea and stomach upset
- Leucopaenia

Tanzeelah now 12 years old

- MMF was not as effective as Tacrolimus. The relapses have been much more frequent
- What to do next?

Treatment of steroid dependent/ frequently relapsing



- Levamisole
- Low dose steroids every other day
- Steroids during infection
- Cyclophosphamide
- Cyclosporine
- Tacrolimus
- Mycophenolate
- **Combination CNI and MMF?**

Treatment of steroid dependent/ frequently relapsing

- Levamisole
- Low dose steroids every other day
- Steroids during infection
- Cyclophosphamide
- Cyclosporine
- Tacrolimus
- Mycophenolate
- Combination CNI and MMF?
- Rituximab

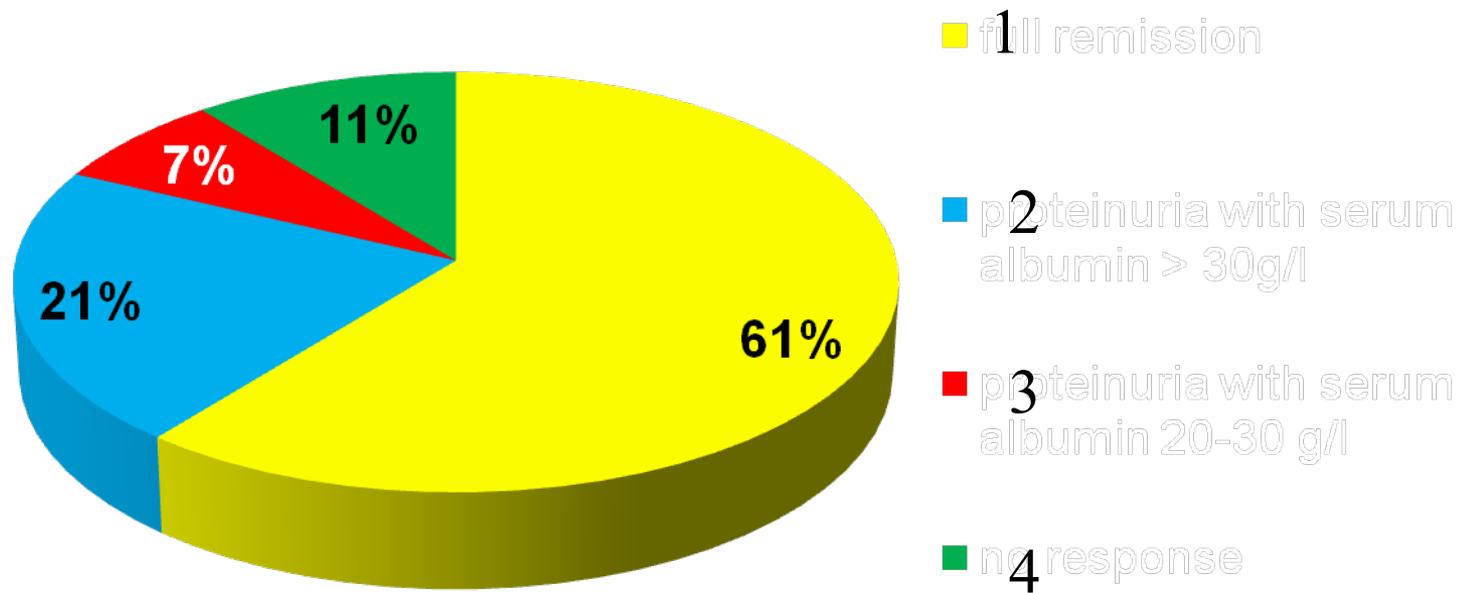
Rituximab in difficult to treat Nephrotic Syndrome



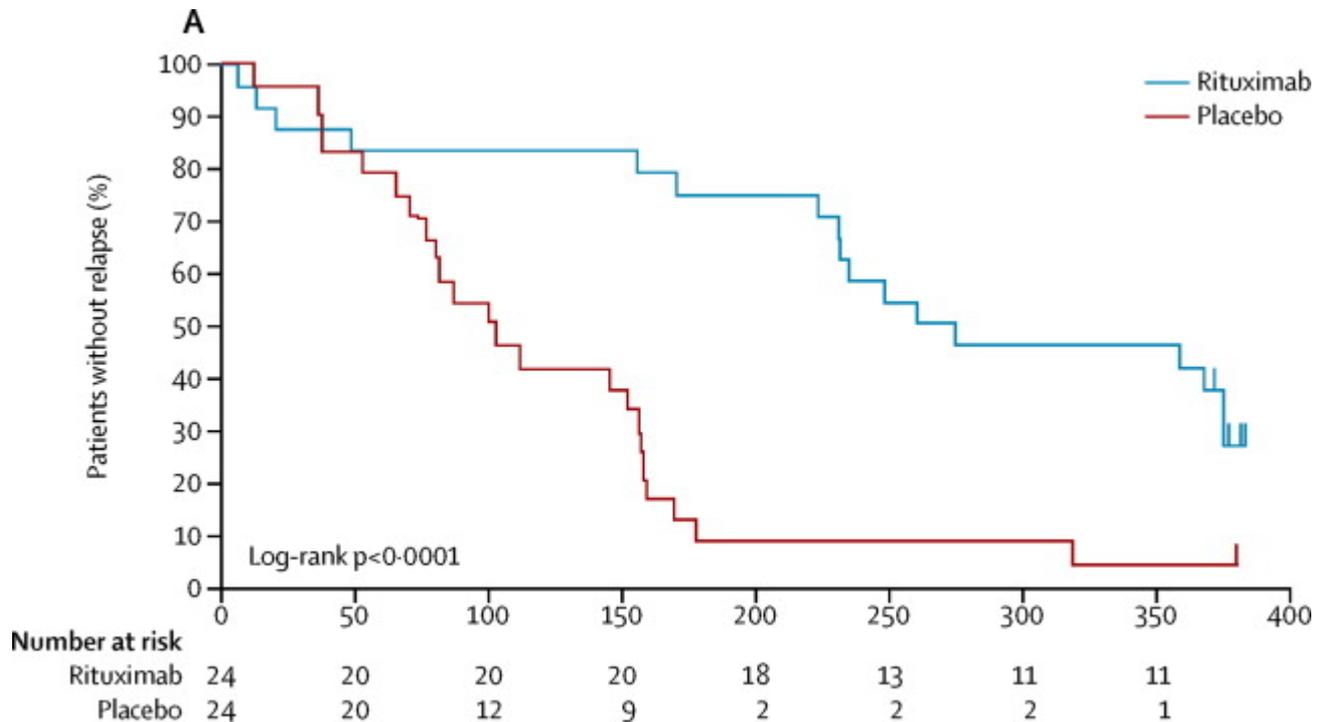
A. Prytuła and K. Tullus

Ped Nephrol 2010;25:461

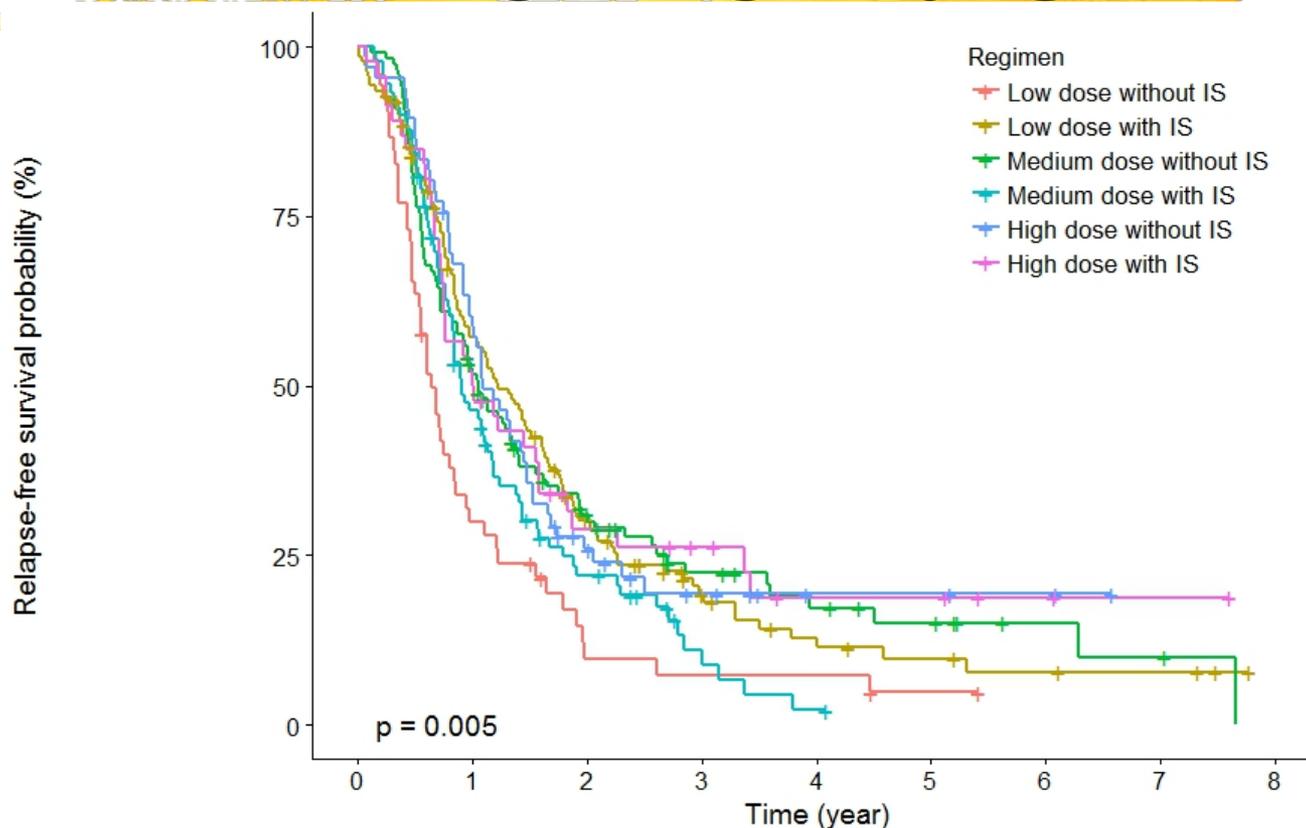
Initial response in SDNS and FRNS



Randomised trial rituximab vs placebo



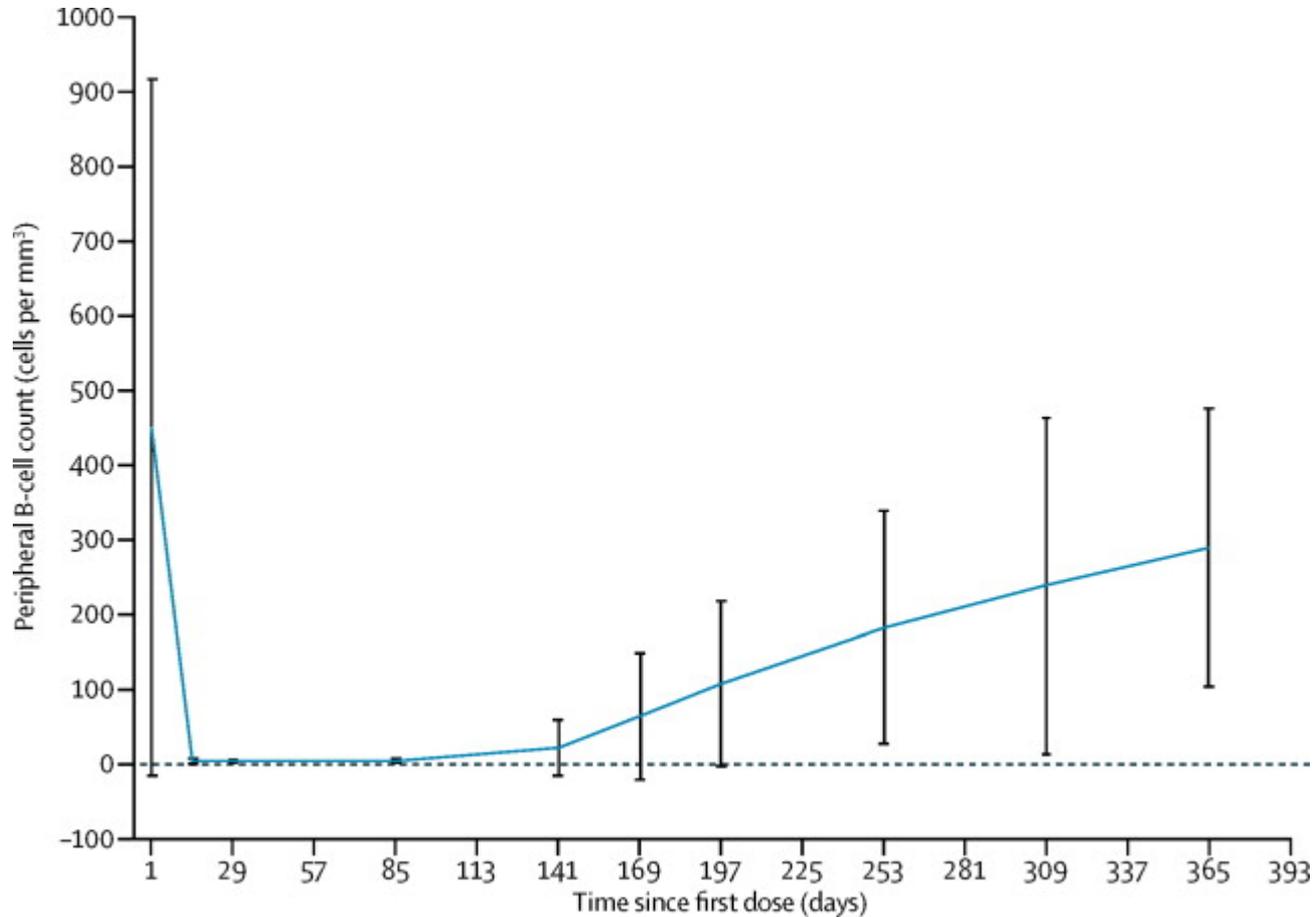
Response to rituximab in 517 children



		Number at risk								
Regimen		0	1	2	3	4	5	6	7	8
	Low dose without IS	52	15	4	3	3	1	0	0	0
	Low dose with IS	139	74	36	17	9	6	4	3	0
	Medium dose without IS	118	60	30	15	10	7	3	2	0
	Medium dose with IS	90	39	16	5	1	0	0	0	0
	High dose without IS	66	39	14	7	3	3	2	0	0
	High dose with IS	46	24	11	8	4	4	2	1	0
		0	1	2	3	4	5	6	7	8

Time (year)

B cell recovery



Side effects



- Infections
 - Myocarditis
 - Pneumocystitis carinii
 - Hepatitis B
- Pulmonary fibrosis - RALI

Summary

- A large number of different therapeutic options exist for children with FRNS and/or SDNS
- This gives many opportunities to obtain the most important goal in these children

To reduce the total steroid burden

- It is not clear at this point which of these treatments is the best