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29 September 2020

Rituximab as a front-line therapy for adult-onset minimal change disease with nephrotic syndrome

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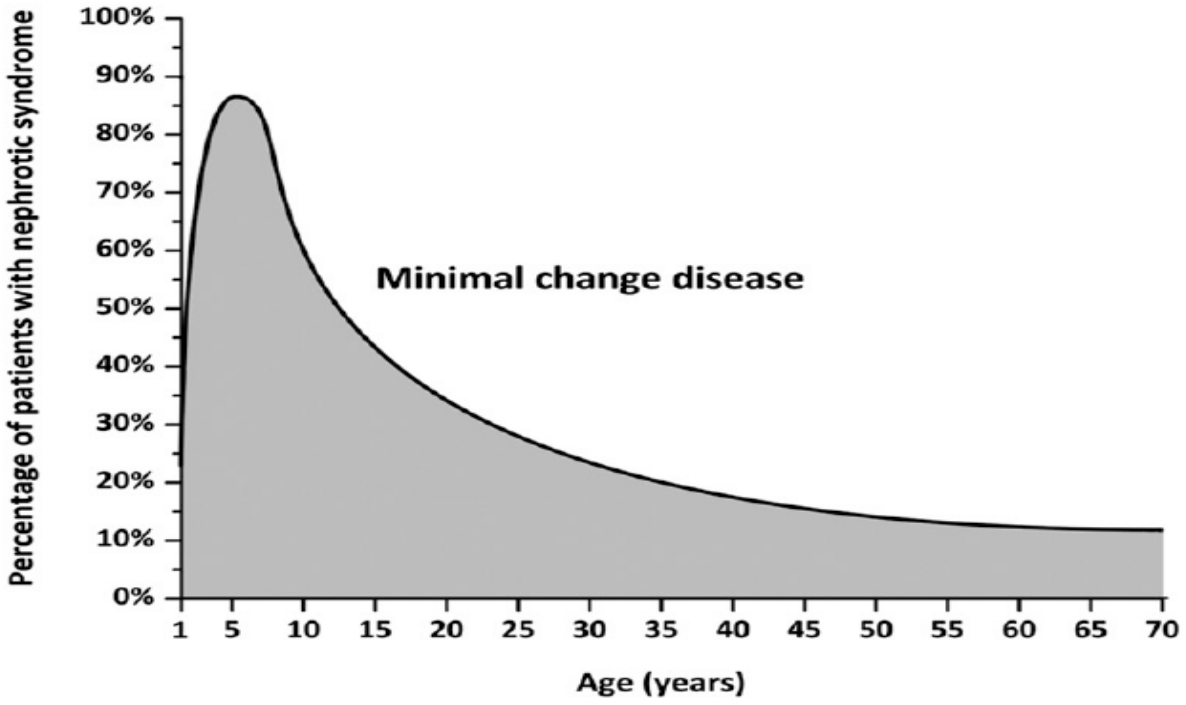
MCD: DEFINITION

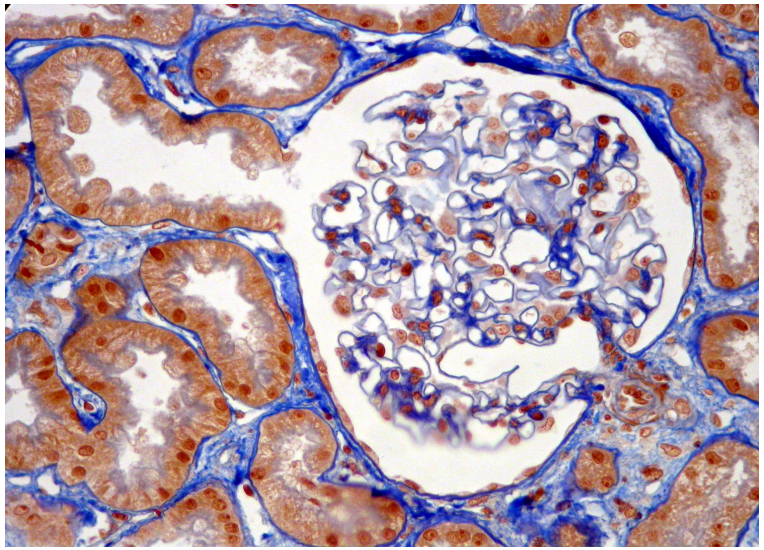


- Commonest cause of NS in children.
- > 90% of cases of NS in children <10 yrs
- 50% of NS cases in adolescents and children >10 yrs
- 10-15% of primary NS in adults

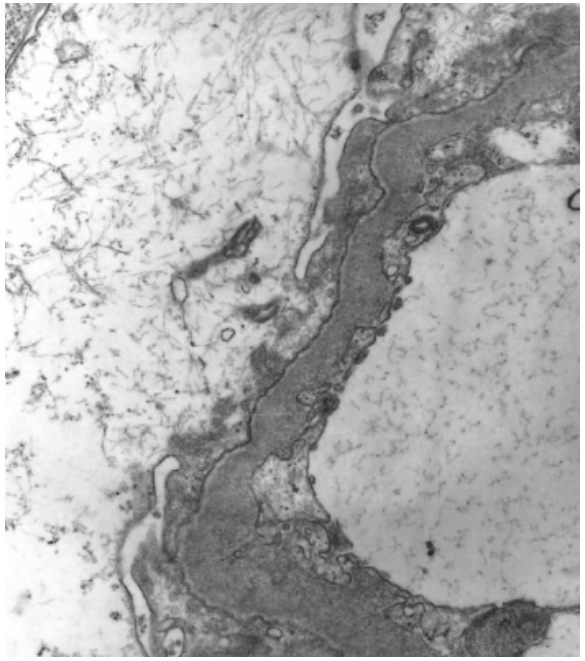
Vivarelli et Al – CJASN - February, 2017

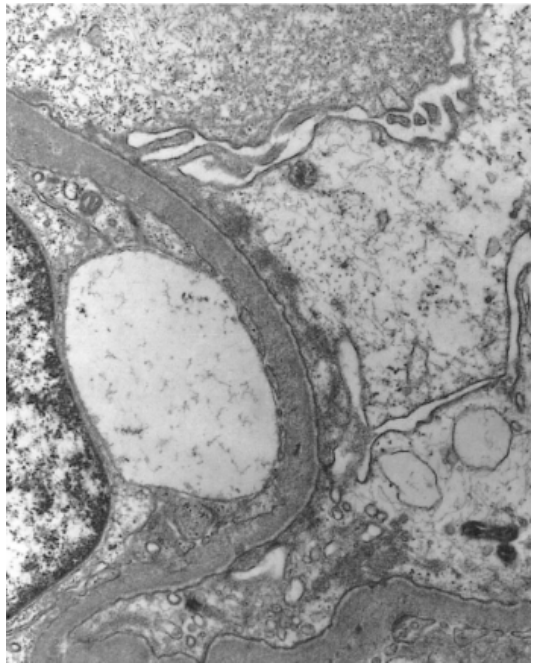
Korbet et Al - Clin J Am Soc Nephrol – June, 2019

HISTOLOGICAL FEATURES



• Minimal change disease is defined by nephrotic syndrome with normal appearing light microscopy





with foot process effacement on electron microscopy in the absence of cellular infiltrates or immune deposits.

ETIOLOGY

- ✓Idiopathic (80-90% of cases)
- ✓Secondary
  - ✓ Drugs – NSAIDs, gold, rifampin, penicillins, trimethadione
  - ✓ Toxins - mercury, lead
  - ✓ Atopic agents - bee stings, poison ivy, pollen
  - ✓ Infection – Syphilis, Infectious mononucleosis, HIV
  - ✓ Tumor - Hodgkin lymphoma (most commonly), other lymphoproliferative diseases, carcinomas
  - ✓ Other glomerular diseases – IgA nephropathy, Lupus, PKD.

Glassock R. NDT 18:p vi52, 2003.

CLINICAL FEATURES

✓ A burden of data deals with course, treatment and outcomes in pediatric patients. Much less is known about adults.

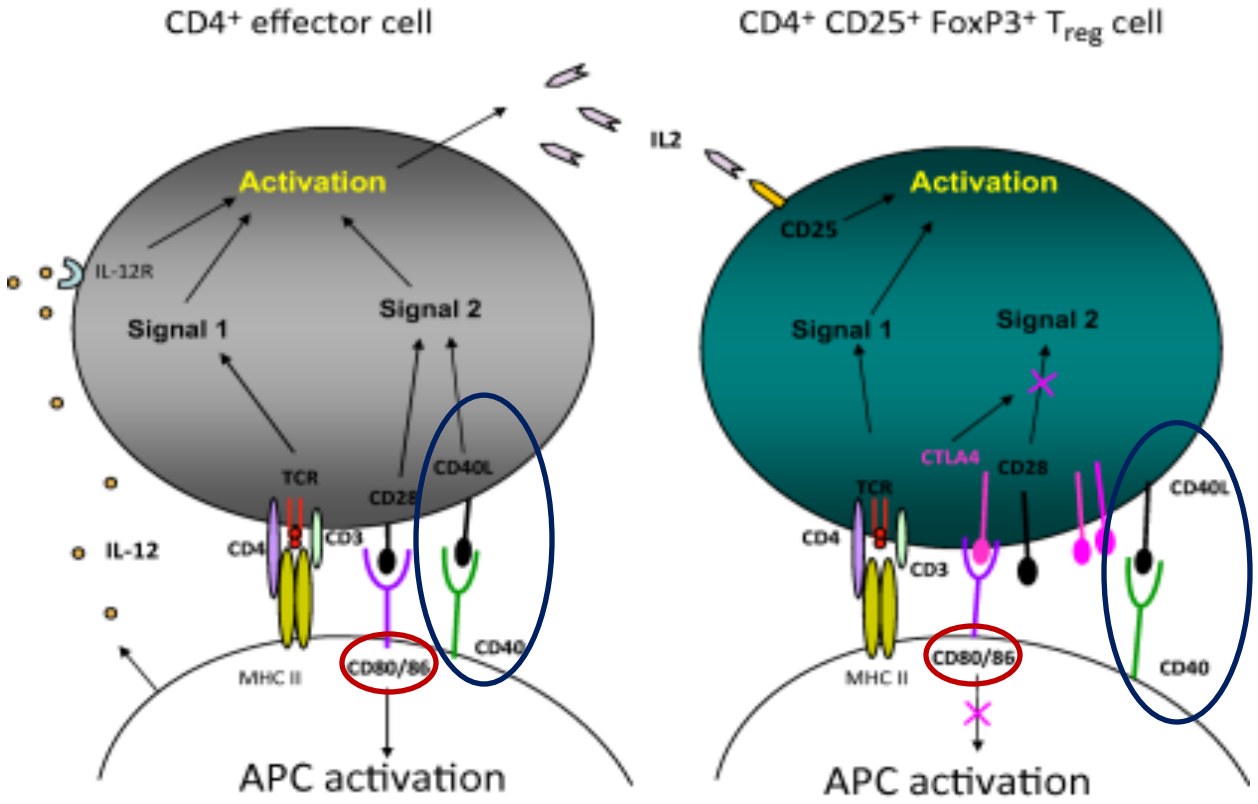
✓ Sudden onset (days to weeks) of nephrotic syndrome

✓ Hypertension (25-50%), hematuria (20-30%) and renal dysfunction (20-25%) more common in adults

✓ Patients with adult-onset MCD may experience progression to ESRD

PATHOGENESIS

Regulatory T cells and minimal change nephropathy: in the midst of a complex network



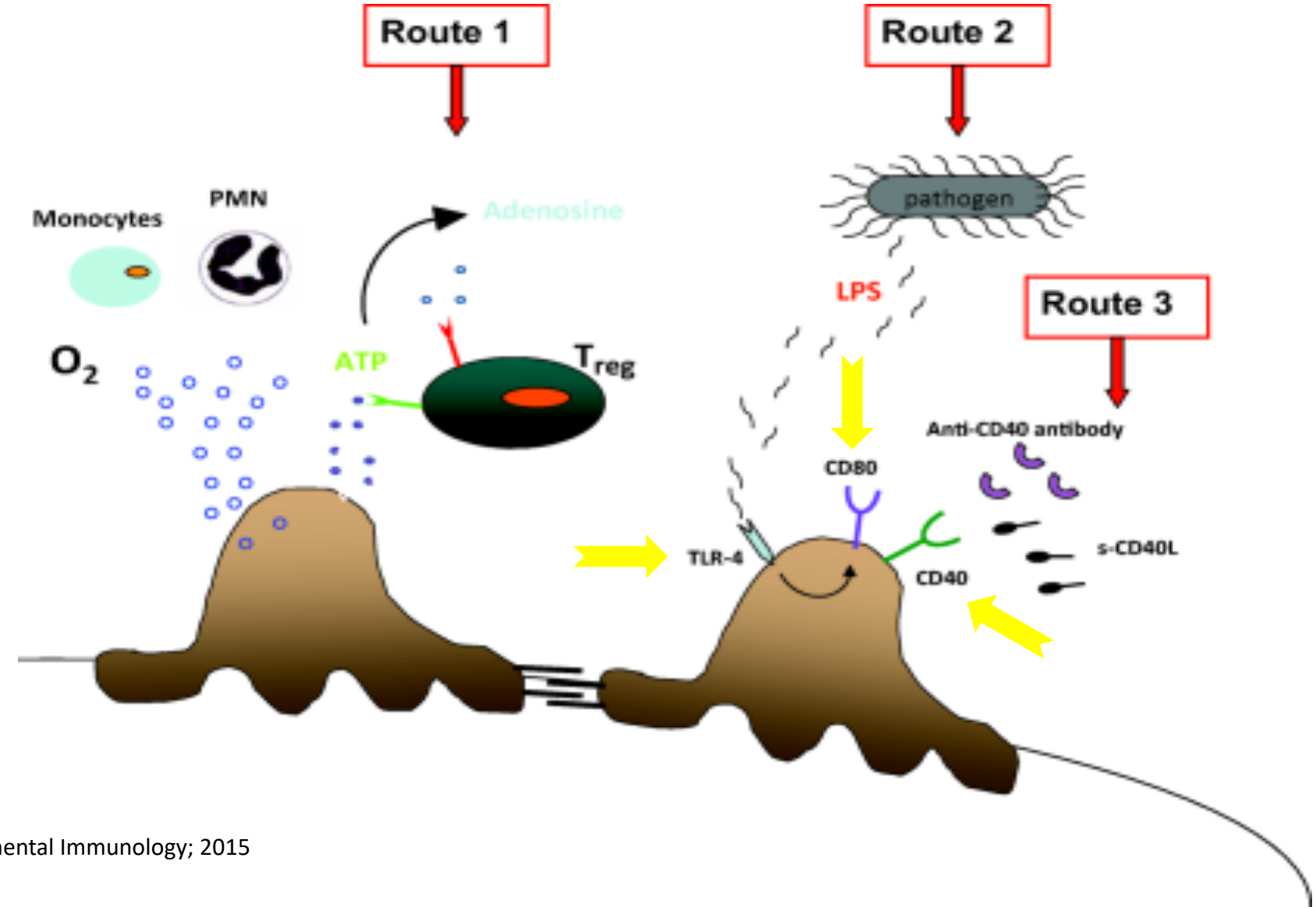
Evolution of basic immunology and therapies provide a complex pathogenetic scenario which include innate immunity, B cells and Tregs

Local factors generated by interleukin-13, toll-like receptors 3 and 4, podocyte-derived CD80, and/or angiopoietin-like 4 protein and influenced by regulatory T cells (CTLA4) have assumed central roles

Bertelli R -Clinical & Experimental Immunology; 2015

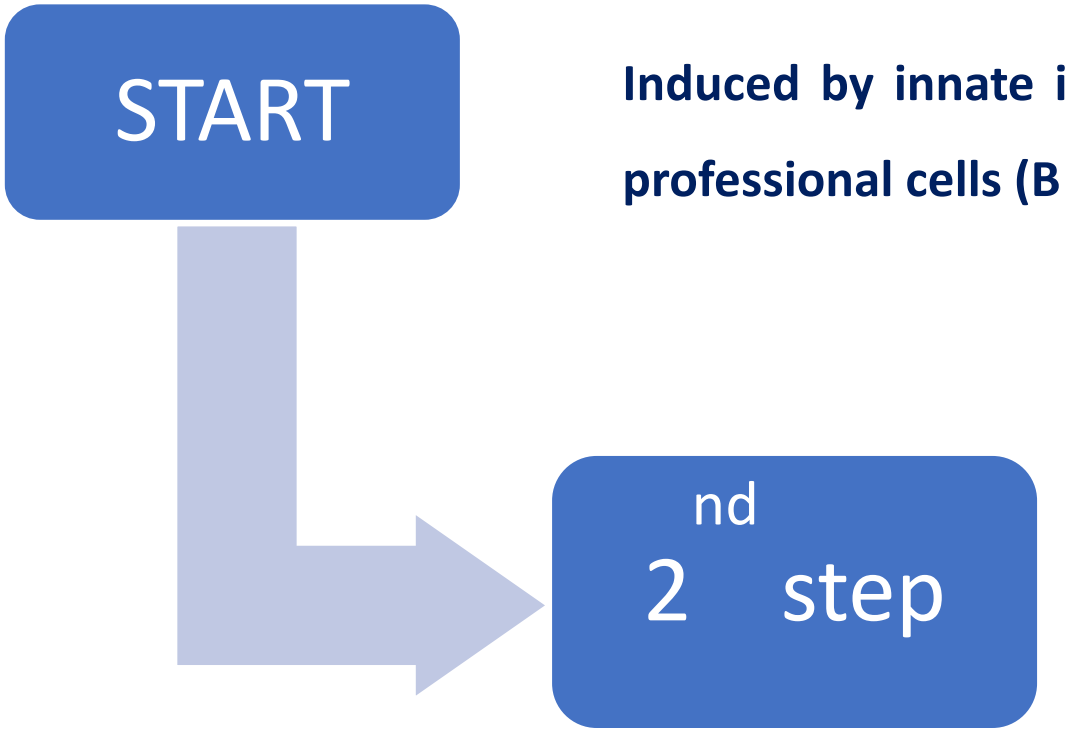
PATHOGENESIS

PODOCYTES AND EARLY IMMUNE RESPONSE



Bertelli R - Clinical & Experimental Immunology; 2015

PATHOGENESIS



Induced by innate immunity with activation of CD80 by professional cells (B cells/TLRs)

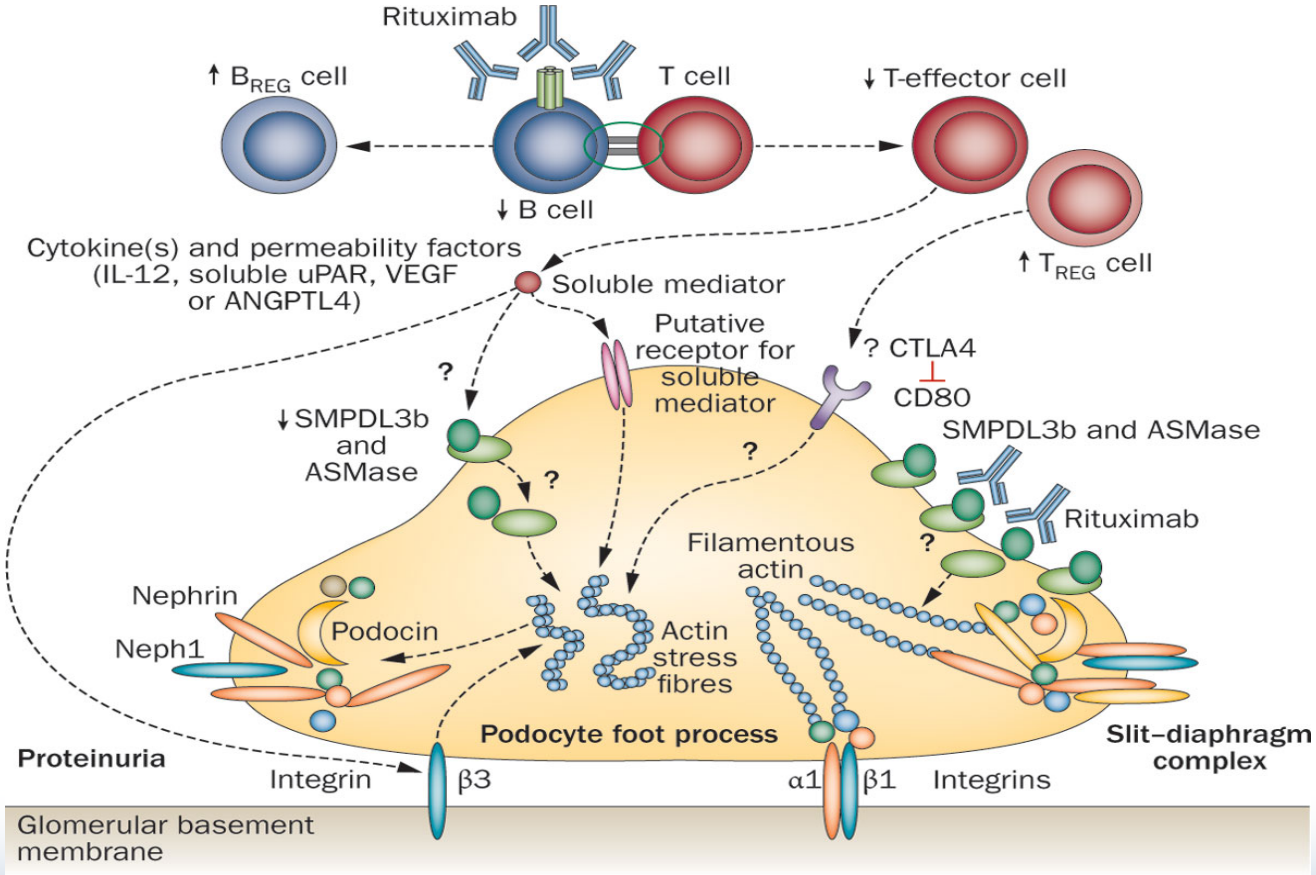
Prevalence of an inflammatory pathway (based on the activation of Teff by IL-7 and IL-2, and of Th17 by IL-6 and TGF-b) podocyte injury

Treg expansion that blunts oxidation by reducing ATP levels and increasing adenosine

Characterizing single cells in each phase of MCN and in relation to therapies is a challenge, and we now have adequate tools for clarifying all single aspects.

Proposed mechanisms of action of RTX in pts with nephrotic syndrome

Considering that RTX effects are supposed to be confined to a subset of circulating and tissue-residing B cells, its efficacy is surprising.



There are many interactions between B and T cells.

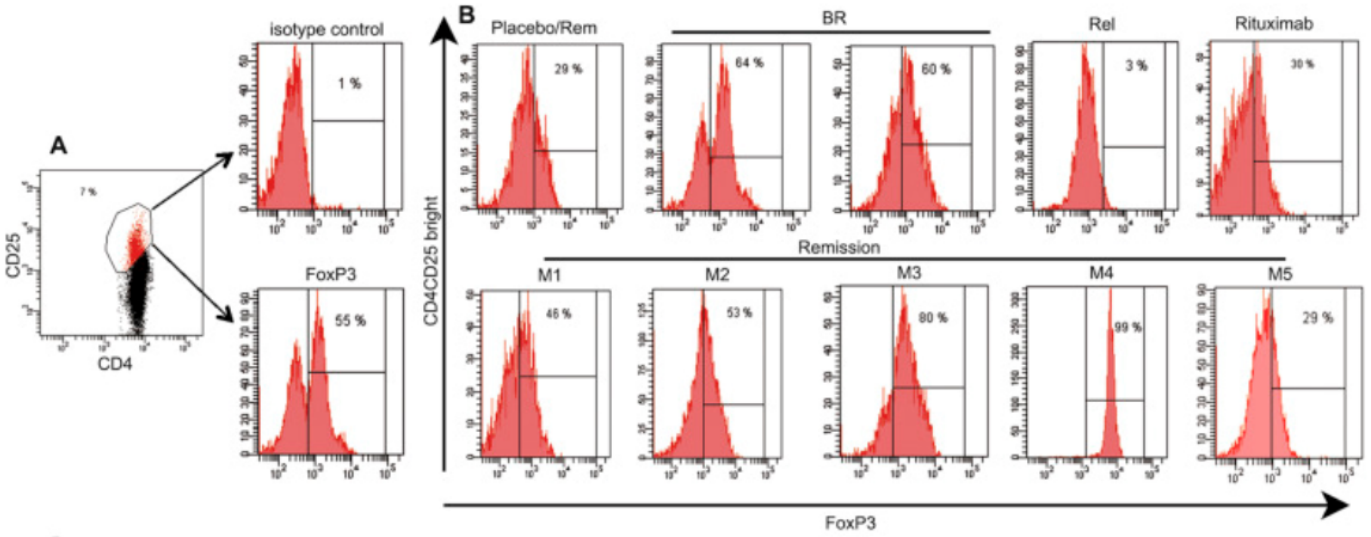
Suppression of B cells could affect the properties of T cells.

A subset of T cells might be the source of the elusive ‘permeability factor’.

nature REVIEWS NEPHROLOGY

Sinha A. & Bagga, A. (2013) Rituximab therapy in nephrotic syndrome: implications for patients’ management

NEPHRUTIX:
A randomized, double-blind, placebo vs Rituximab-controlled trial assessing T-cell subset changes in Minimal Change Nephrotic Syndrome



✓ Relapses are associated with inhibition of IL2 production and a loss of Treg cells,

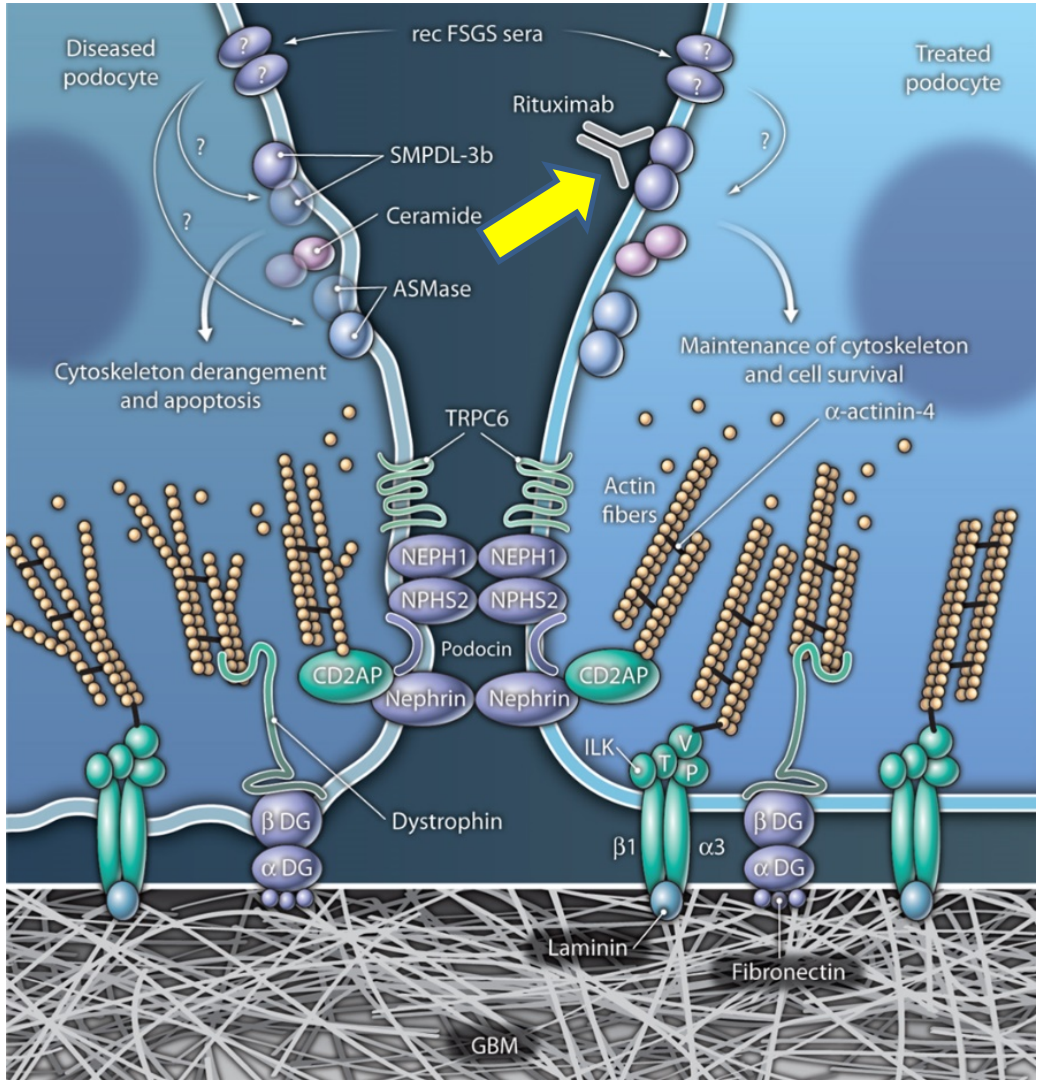
✓ Remissions are associated with downregulation of a T-cell subset involved in innate immunity.

✓ The new T-cell subsets identified in this study might have a potential impact on T cell-B cell cooperation.

✓ This latter could be targeted by Rituximab therapy and highlights this disease as a disorder of innate and adaptive immune response.

Boumediene A et al ; J Autoimmun. 2018 Mar

SUGGESTED MODEL OF DIRECT ACTIVITY OF RTX ON PODOCYTES



It has been shown that **RTX bound to the sphingomyelin phosphodiesterase acid-like 3b protein (SMPDL-3b) of podocytes** suggesting a putative regulation of acid sphingomyelinase (AMSase) activity with stabilization of **podocyte cytoskeleton and** possible mitigation of **apoptosis**

One may speculate that RTX acts locally on podocyte integrity and that this effect correlates with B-cell levels in the circulation

Andrew C. Chan - Sci Transl Med

Rituximab in MCD

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Munyentwali et al[9]	Retrospective case series	17 patients with steroid-dependent or frequently relapsing MCD	Variable: 15 patients with 1–4 weekly infusions at 375 mg/m^2 Two patients with 1 g on days 1 and 15 Patients received additional doses of rituximab if CD19 recovery	Response to rituximab and relapses Reduction of IS treatments Adverse events	65% of patients did not relapse (mean f/u of 26.7 months) 70% of patients achieved withdrawal of steroids and other drugs after 12 months No hematological or infectious complications during follow-up
Guitard et al[10]	Retrospective chart review	41 patients with steroid-dependent or frequently relapsing MCD 51% with nephrotic syndrome	Variable: 21 patients received 1 g on days 1 and 15 12 patients received 4 weekly infusions (375 mg/m^2) One received 1 g once Five received 2 weekly infusions of 375 mg/m^2 Two received 3 weekly infusions of 375 mg/m^2	Complete clinical response: CR (UPCR <0.3 g/g) + withdrawal of all IS treatments Partial clinical response: CR + withdrawal of at least one IS drug Side effects	61% of patients achieved complete clinical response 17% of patients achieved partial clinical response No serious adverse events during follow-up
Takei et al[11]	Prospective, cohort study, with historical controls	25 patients with steroid-dependent and frequently relapsing MCD	375 mg/m^2 twice at an interval of 6 months	Patients with relapse 12 months after rituximab as compared to 12 months before rituximab therapy Side effects	4/25 patients relapsed, as compared to 25/25 patients before rituximab Mild infusion reactions in three patients, one exanthema, and one leukopenia
Iwabuchi et al[12] (follow-up of Takei et al[11])	Prospective, cohort study, with historical controls	25 patients with steroid-dependent and frequently relapsing MCD	375 mg/m^2 every 6 months for 24 months After 24 months, 20 patients continued rituximab every 6 months (treatment continuation group), and five patients discontinued rituximab (treatment discontinuation group)	Number of relapses before and after rituximab therapy CR: urine protein excretion of <0.3 g/day Side effects	108 episodes of relapse in the 24 months before rituximab, and eight episodes during the 24 months after CR maintained in all patients at 24 months 1/5 of treatment discontinuation group developed relapse at 8 months after last rituximab infusion No hematological or infectious side effects

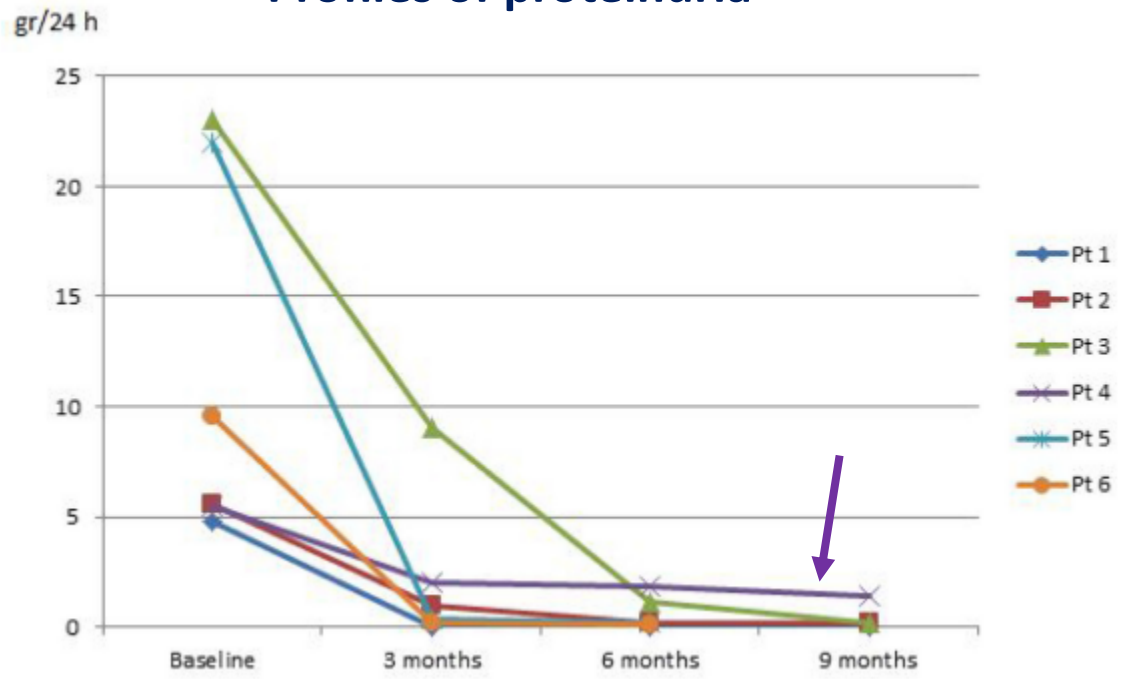
Abbreviations: CR, complete remission; IS, immunosuppressive; MCD, minimal change disease; UPCR, urine protein over creatinine ratio; f/u, follow up.

Rituximab as a front-line therapy for adult-onset minimal change disease with nephrotic syndrome

Table 1: Demographic and clinical baseline characteristics of patients

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6
Sex	F	M	M	F	F	F
Age at diagnosis (years)	45	59	72	61	73	66
Duration of follow-up (months)	36	34	30	12	8	9
Urinary protein (g/day)	4.8	5.6	23	5.5	22	9,6
Albumin (g/dL)	2.1	2.3	1.3	2.9	1.7	2
Total cholesterol (mg/dL)	347		325	416	468	208
Creatinine (mg/dL)	0.8	1.6	3.2	0.5	5	0.6
White blood cell count (u/mm^3)	4.280	8.280	6.210	8.930	9420	7190
Lymphocytes (×1000/ul)	1070	1010	1480	1420	603	2380
CD19 (/mm^3)	77 (7.19%)	42 (4.15%)	148 (10%)	258 (12.8%)	96 (16%)	229 (8.3%)
CD20 (/mm^3)	77 (7.17%)	42 (4.15%)	145 (9.84%)	255 (12.7%)	96 (16%)	229 (8.3%)
IgG (mg/dL)	373	794	229	1414	184	537
IgA (mg/dL)	124	137	181	130	152	146
IgM (mg/dL)	221	42	99	37	298	165

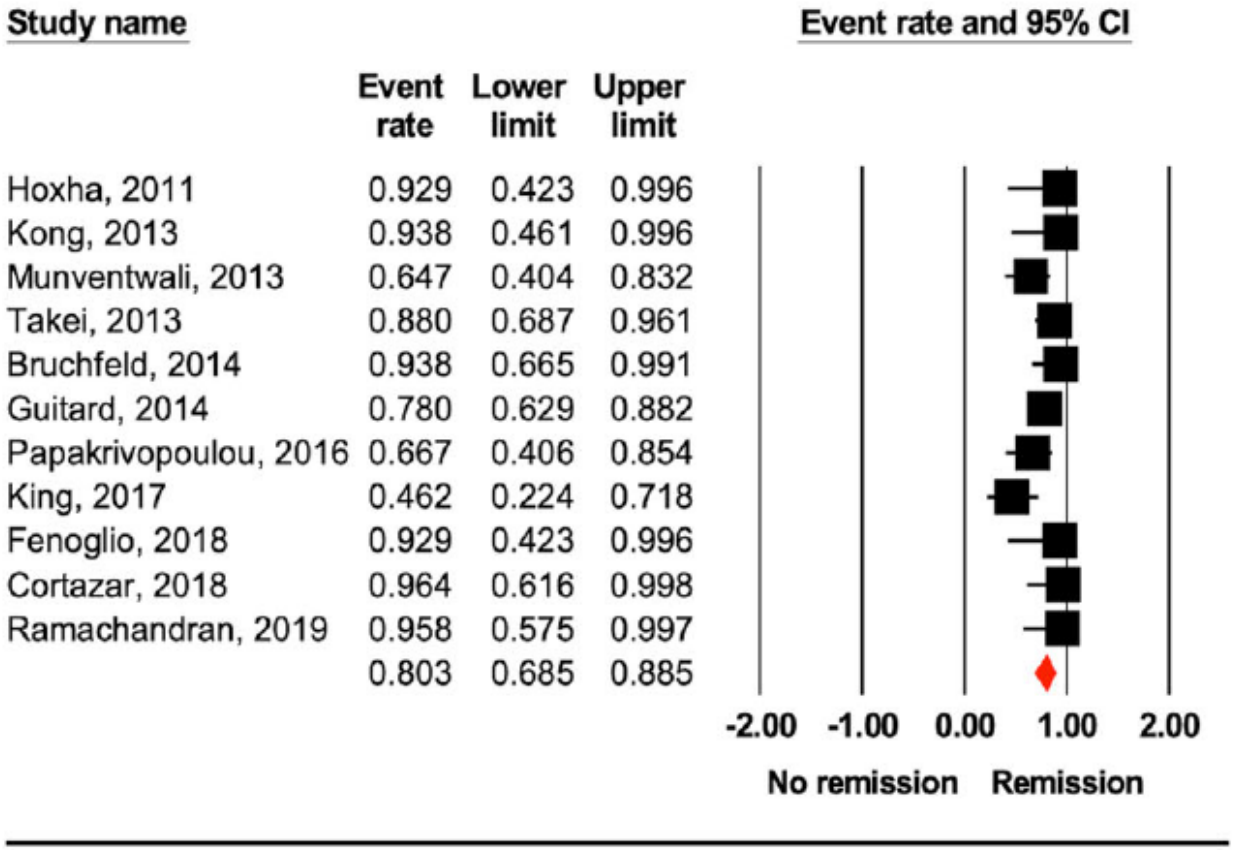
Profiles of proteinuria



Fenoglio et al. - Oncotarget. 2018

TREATMENT OUTCOMES OF RTX THERAPY

Meta-analysis of MCD and overall remission



The overall remission rate was 80.3%

(95% CI, 68.5–88.5%; I2 = 46.4%).

Complete remission rate was 74.7%

(95% CI, 62.5–84.0%; I2 = 15.5%)

Partial remission was 5.6%

(95% CI, 9.9–24.8%; I2 = 0%)

Hansrivijit et al. BMC Nephrology (2020)

Emerging therapeutic strategies for MCD

KDIGO Adults 2019

- 16 weeks of high dose **CS** as a **first line** therapy for MCD (albeit controversial for potential for toxicity)
- **CNIs** or **CYC** as **second line**
- **MMF** as **third** in steroid-dependent MCD
- **RTX** is **emerging as a second line** therapy in MCD

Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Rovin BH and Conference PartecipantKidney Int. 2019

Randomized controlled trials are underway to investigate the value of RTX in adult MCD (Efficacy of Rituximab in Comparison to Continued Corticosteroid Treatment in Idiopathic Nephrotic Syndrome; NCT03298698)

Is maintenance therapy necessary for all pts

S. A. - male - 19 yrs

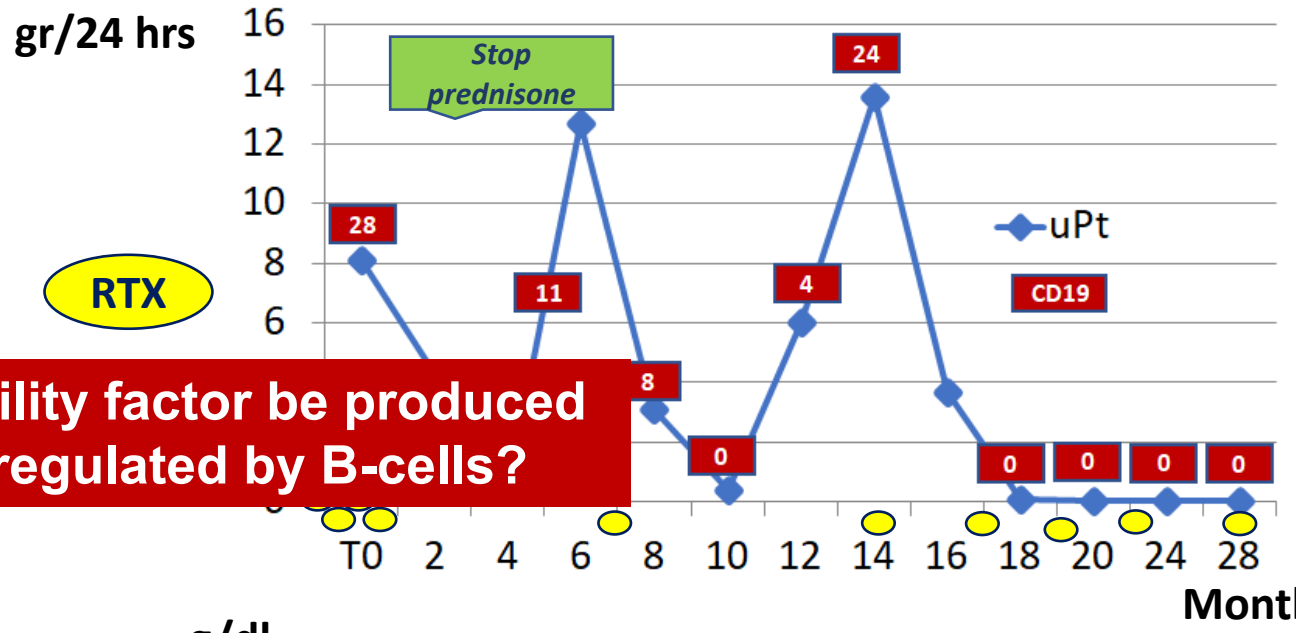
Onset Age: 16 months

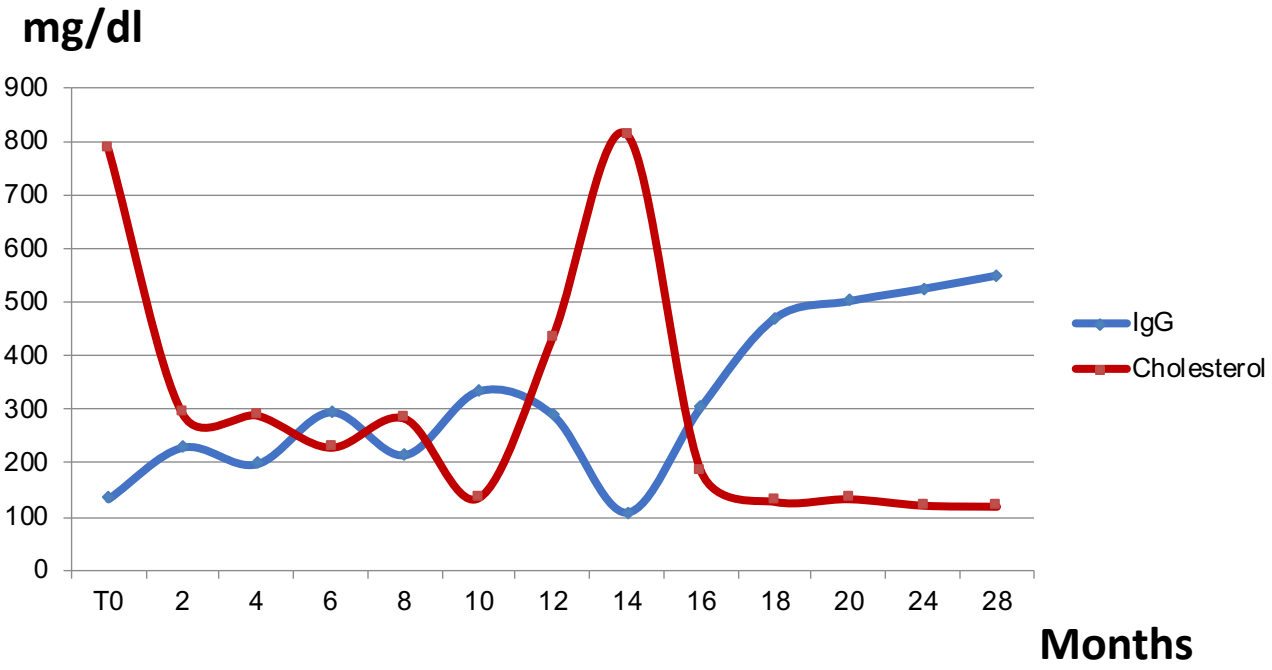
Previous therapies:

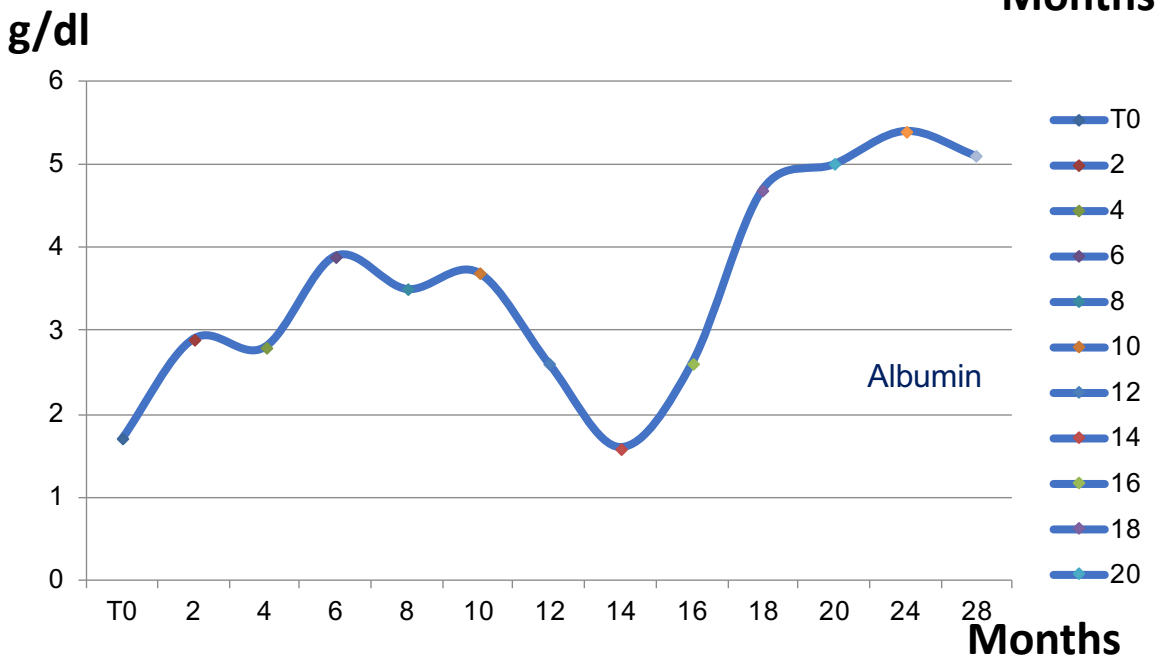
- ***CyA***
- ***MMF***
- ***TAC***
- ***GCS***
- ***RTX 1 in***

Prednisone min dose: 5 mg/die

Could the permeability factor be produced through pathways regulated by B-cells?

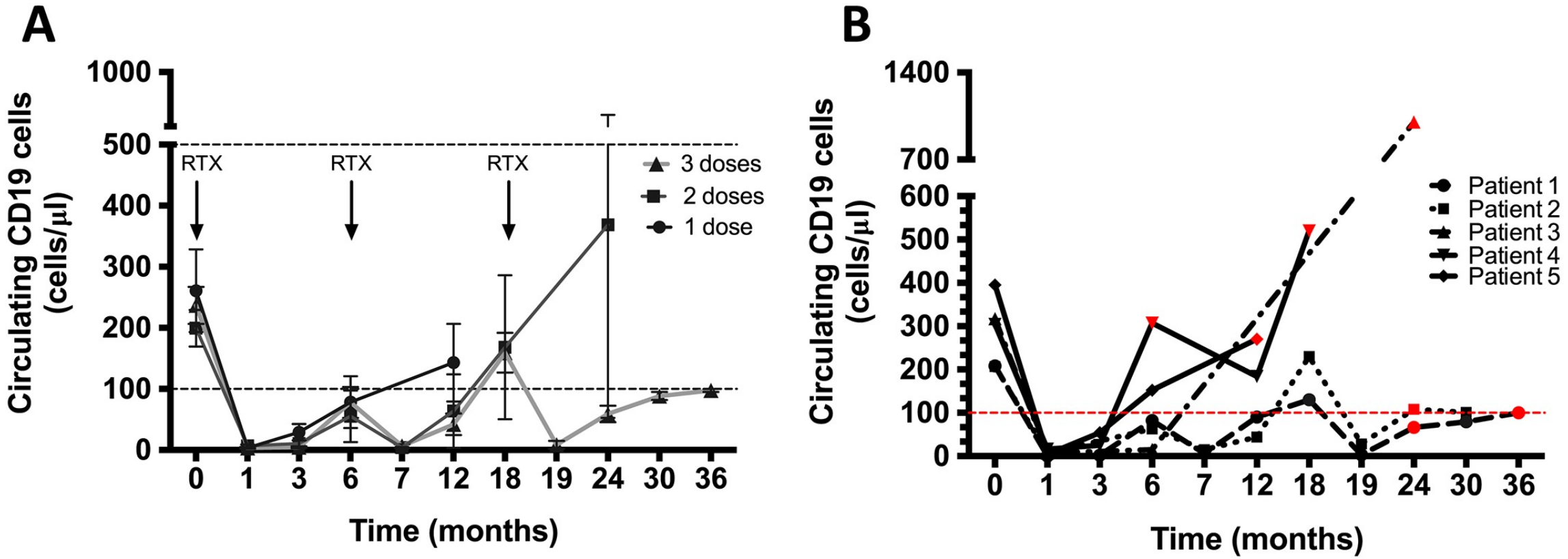






CD19+ and MCD relapse *in children*

Effective treatment with rituximab for the maintenance of remission in frequently relapsing minimal change disease



Most relapses (five of seven) occurring with CD19 counts of 100 cells/µl or greater

Papakrivopoulou E - Nephrology, 2016

Efficacy of repeat-dose rituximab maintenance therapy for minimal change disease in adults

Prospective trial of RTX maintenance therapy in 25 adults with SDNS

Patients were administered single doses of 375 mg/m^2 RTX every 6 months.

Total number of relapses and dose of prednisolone were reported to be decreased following administration of RTX

✓ most participants in the study were young adults (mean age 30 ± 12 yrs)

Tagichi S - Nephrol Dial Transplant. 2013

G.F. - male - 72 yrs

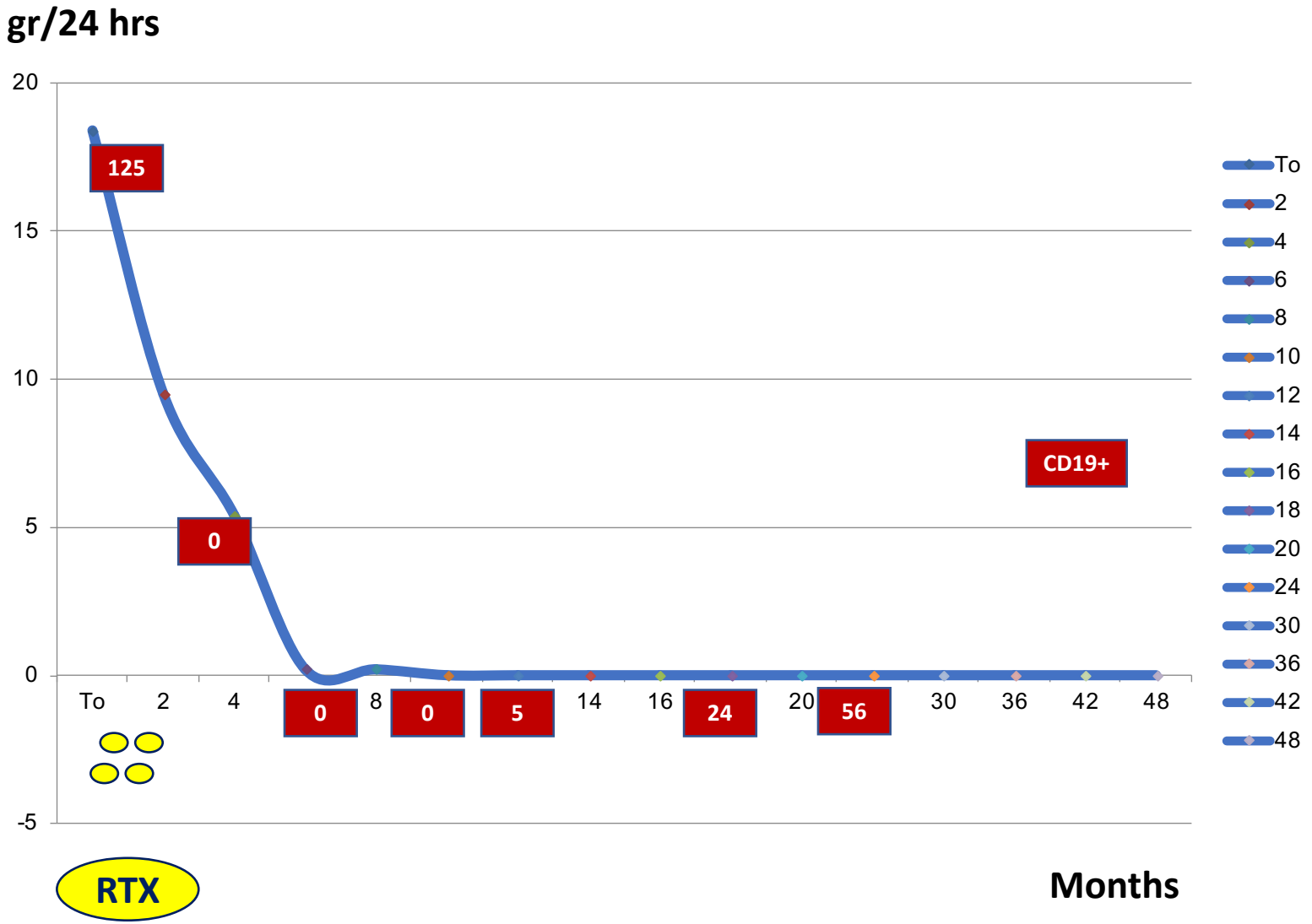
Onset Age: 72 yrs

Overweight

Hypertension

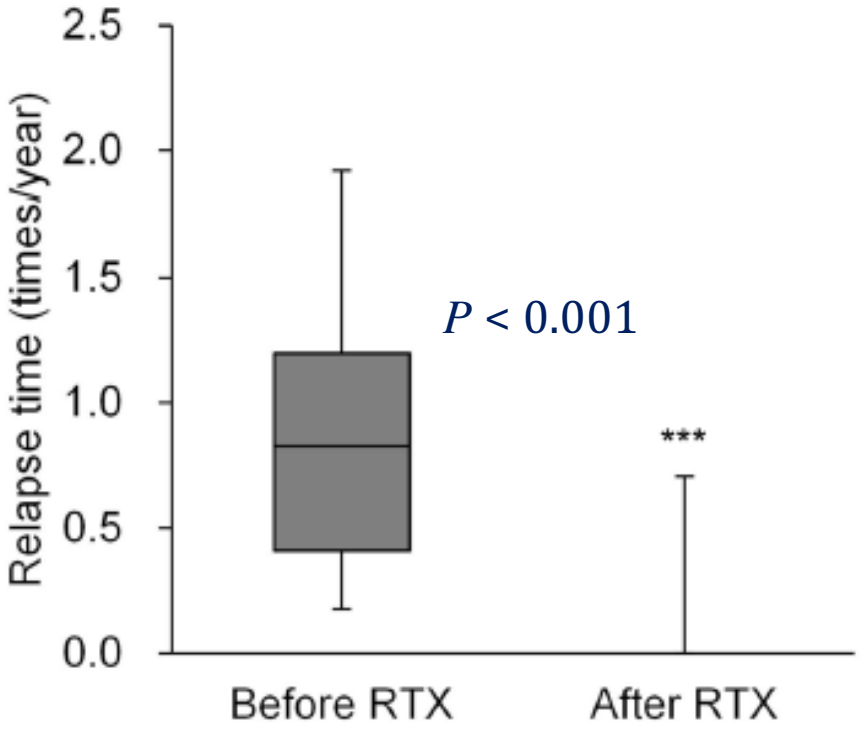
Diverticulosis

No previous therapies



Efficacy of repeat-dose rituximab maintenance therapy for minimal change disease in adults

13 adults with biopsy-proven MCD in remission with prednisolone or immunosuppressants or both, who had received repeat-dose RTX.



- ✓ In all pts, median relapse frequency decreased significantly from 0.83 (0.18–1.92) to 0 (0–0.71) times/year after RTX induction
- ✓ Dose of concomitant steroids was greatly reduced
- ✓ No serious adverse events

Remission was maintained not only during RTX treatment but also after discontinuation for a median observation period of 28 (16–60) months after RTX initiation

Taguchi et al - Clinical and Experimental Nephrology, Aug 2020

On the basis of the reported results, should we prescribe RTX maintenance therapy to all patients?

RTX MONOTHERAPY AS FRONT LINE THERAPY

	PT1	PT2	PT3	PT4**	PT5	PT6	PT7	PT8	PT9	PT10	PT11*	PT12*
Age	45	59	72	61	73	66	23	19	83	28	20	36
Follow-up (months)	60	58	54	36	32	33	12	24	24	19	10	32
uPT (gr/day)	4.8	5.6	23	5.5	22	9.6	3.7	3.6	10.8	4.3	13	10
Albumin (gr/dl)	2.1	2.3	1.3						1.9	2.3	1.5	2.2
sCrs (mg/dl)	0.8	1.6	3.2	0.5	5	0.6	0.6	1.2	3.8	0.6	1.5	0.7
CD19+ /mm^3	77	42	148	258	96	229	215	236	50	273	140	245
IgG (mg/dl)	373	794	229	550	184	537	519	545	558	202	240	425

9 out of 12 patients experienced no relapse

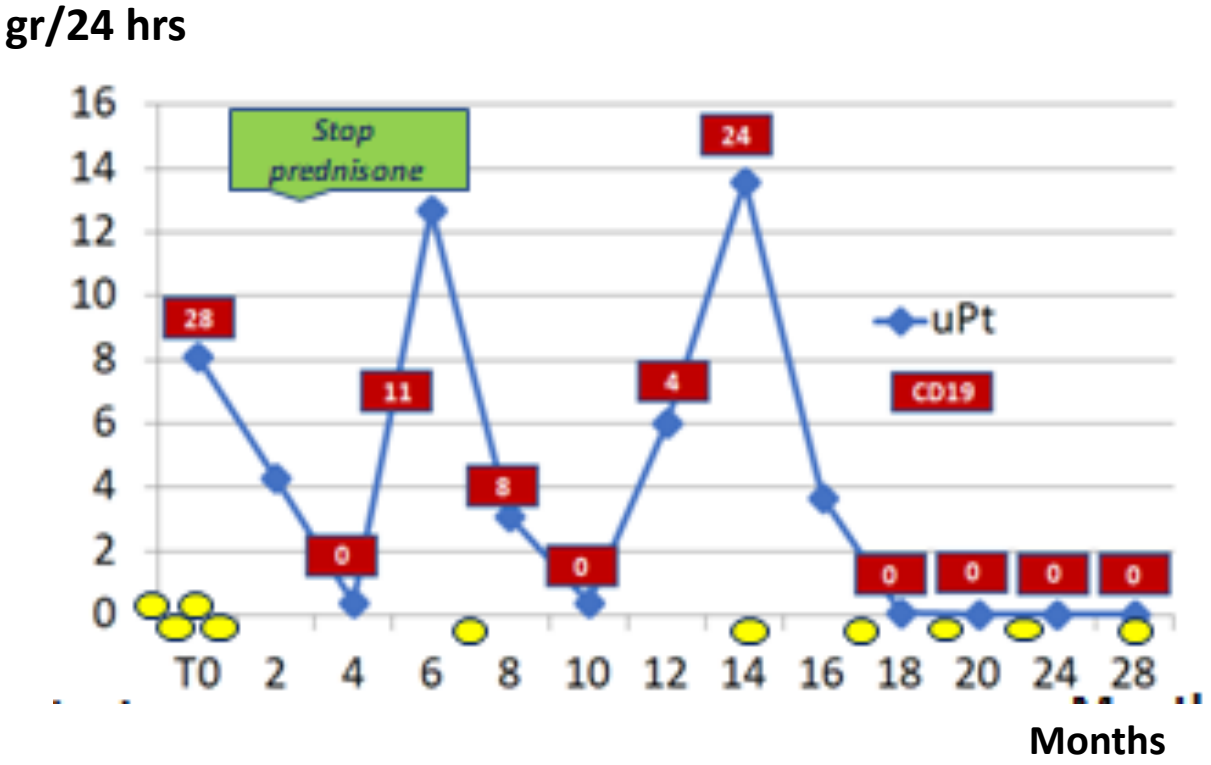
- ✓ All but 1 (#pt 4) achieved a complete remission
- ✓ Pt 4 achieved a complete remission after a 2nd cycle of RTX (15 months later)
- ✓ *2 pts (#11,12) relapsed after 24 and 10 months respectively. #pt12 was retreated with 1 dose of RTX and achieved a complete response again. # pt11 started a second Cycle of RTX that's ongoing

Manuscript under submission

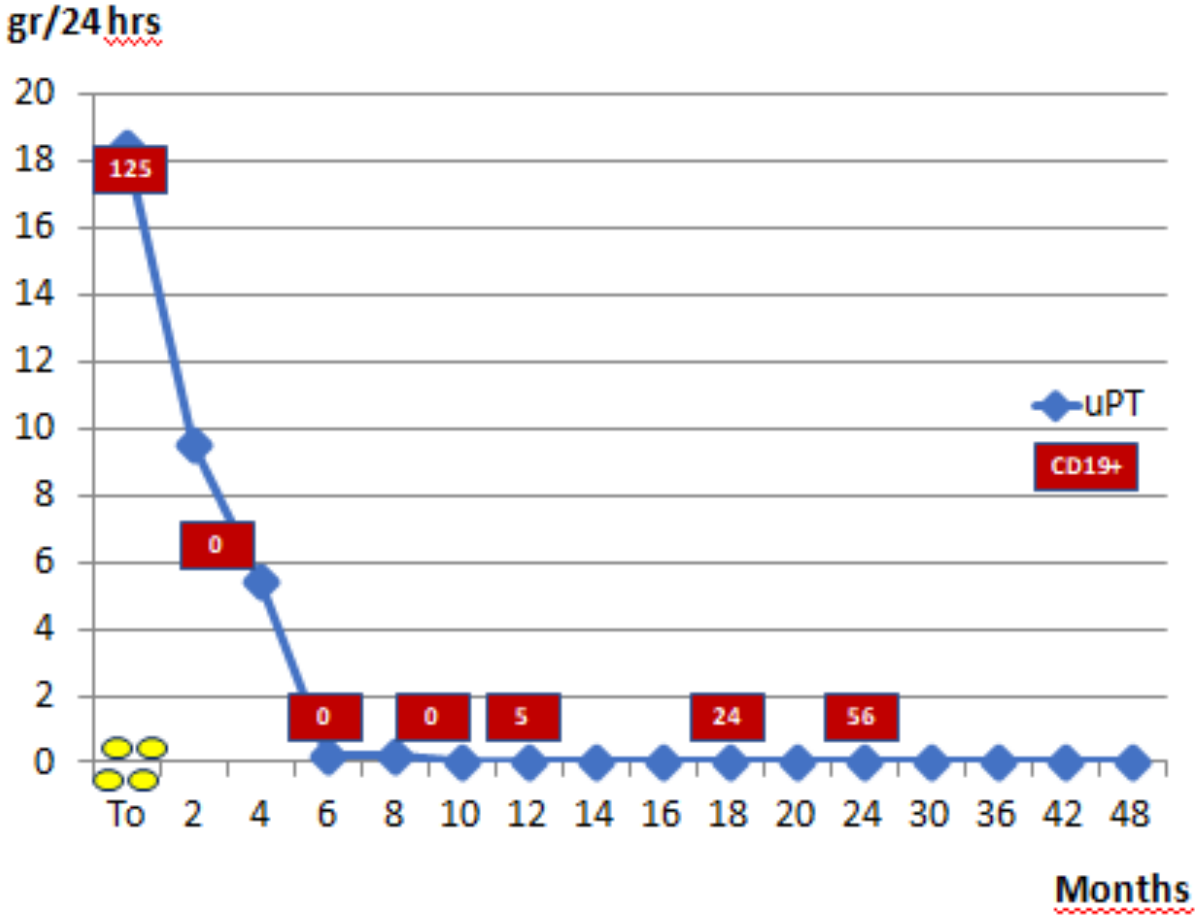
On the basis of the reported results, should we then prescribe RTX maintenance therapy to all patients?

Probably NOT

How can we decide which is the optimal protocol for our patients?



Is age at disease onset the difference?



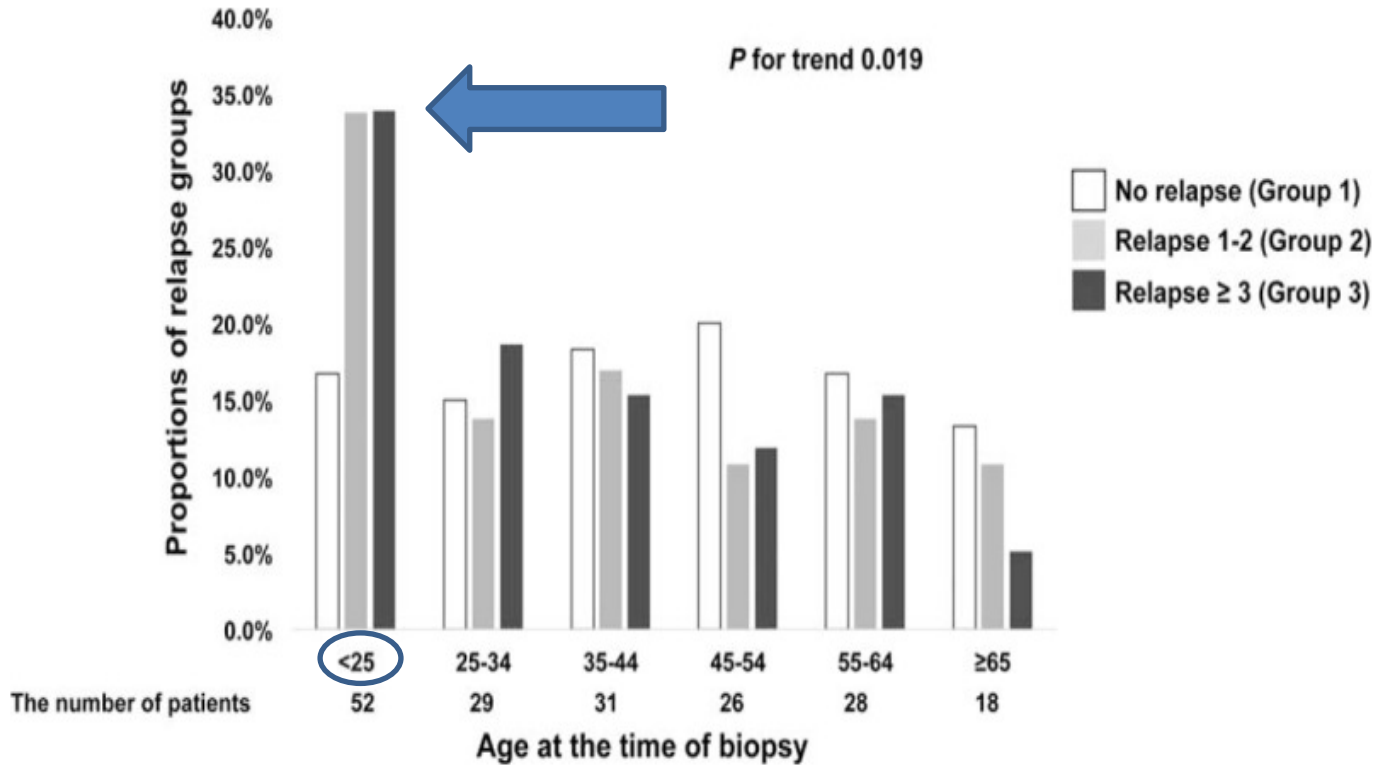
Can the RTX protocol be the same for these 2 pts?

Predictors of relapse in adult-onset MCD patients

On univariate analysis:

- younger onset age,
- lower serum albumin level
- mesangial proliferation grade,
- initial treatment without CYC
- shorter treatment duration,
- longer follow-up duration

Distribution of relapse groups in 10-year age groups



Lee H et al - Medicine, Mar 2016

RTX MONOTHERAPY AS FRONT LINE THERAPY

	PT1	PT2	PT3	PT4**	PT5	PT6	PT7	PT8	PT9	PT10	PT11*	PT12*
Age	45	59	72	61	73	66	23	19	83	28	20	36
Follow-up (months)	60	58	54	36	32	33	12	24	24	19	10	32
uPT (gr/day)	4.8	5.6	23	5.5	22	9.6	3.7	3.6	10.8	4.3	13	10
Albumin (gr/dl)	2.1	2.3	1.3	2.9	1.7	2	1.5	1.4	1.9	2.3	1.5	2.2
sCrs (mg/dl)	0.8	1.6	3.2	0.5	5	0.6	0.6	1.2	3.8	0.6	1.5	0.7
CD19+ /mm^3	77	42	148	258	96	229	215	236	50	273	140	245
IgG (mg/dl)	373	794	229	550	184	537	519	545	558	202	240	425

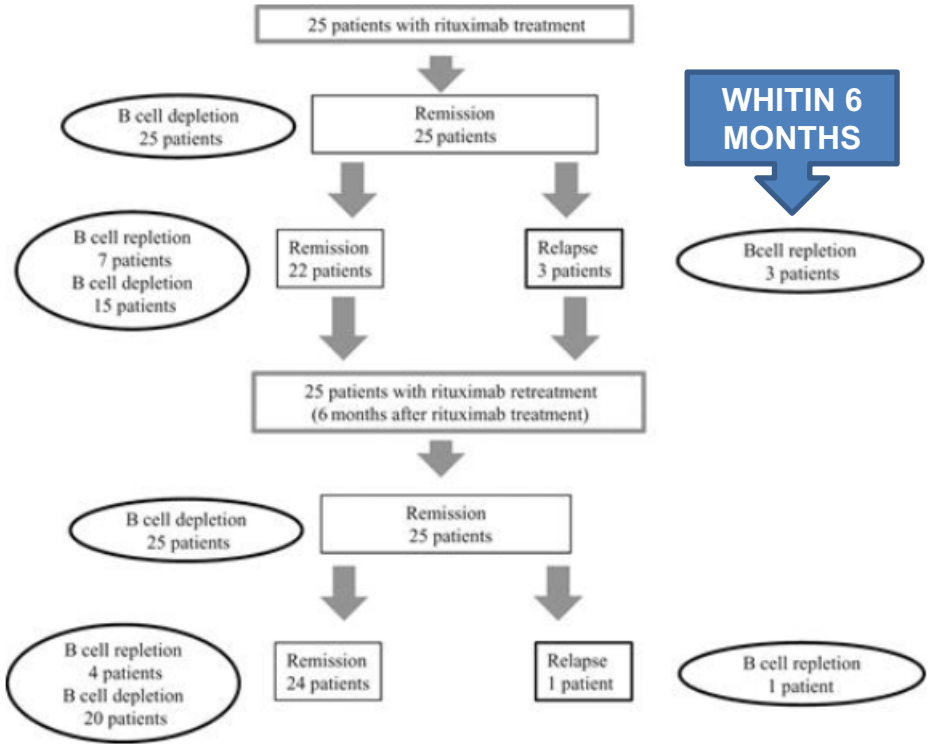
- Younger Age Onset
- Lower seum Albumin level
- Mesangial Poliferation rate
- Shorter treatment duration
- Longer follow up duration

Manuscript under submission

Is a low dose of RTX enough for adult-onset MCD

Effect of single-dose RTX on steroid-dependent minimal-change nephrotic syndrome in adults

Clinical follow-up after rituximab treatment.



	Pre-rituximab	Post-rituximab	P-value
PSL(*n*)	25	4	<0.001
The cumulative dose of PSL (g)	8.2 ± 3.4	3.3 ± 2.3	<0.001
CyA (*n*)	20	6	<0.001
MMF (*n*)	3	0	0.2
MZ (*n*)	5	0	0.05
Relapse (*n*)	25	4	<0.001

All 16 pts with nephrotic syndrome or partial remission at the start of RTX treatment had complete remission within 1 month.

Takei T.- Nephrology Dialysis Transplantation 2013

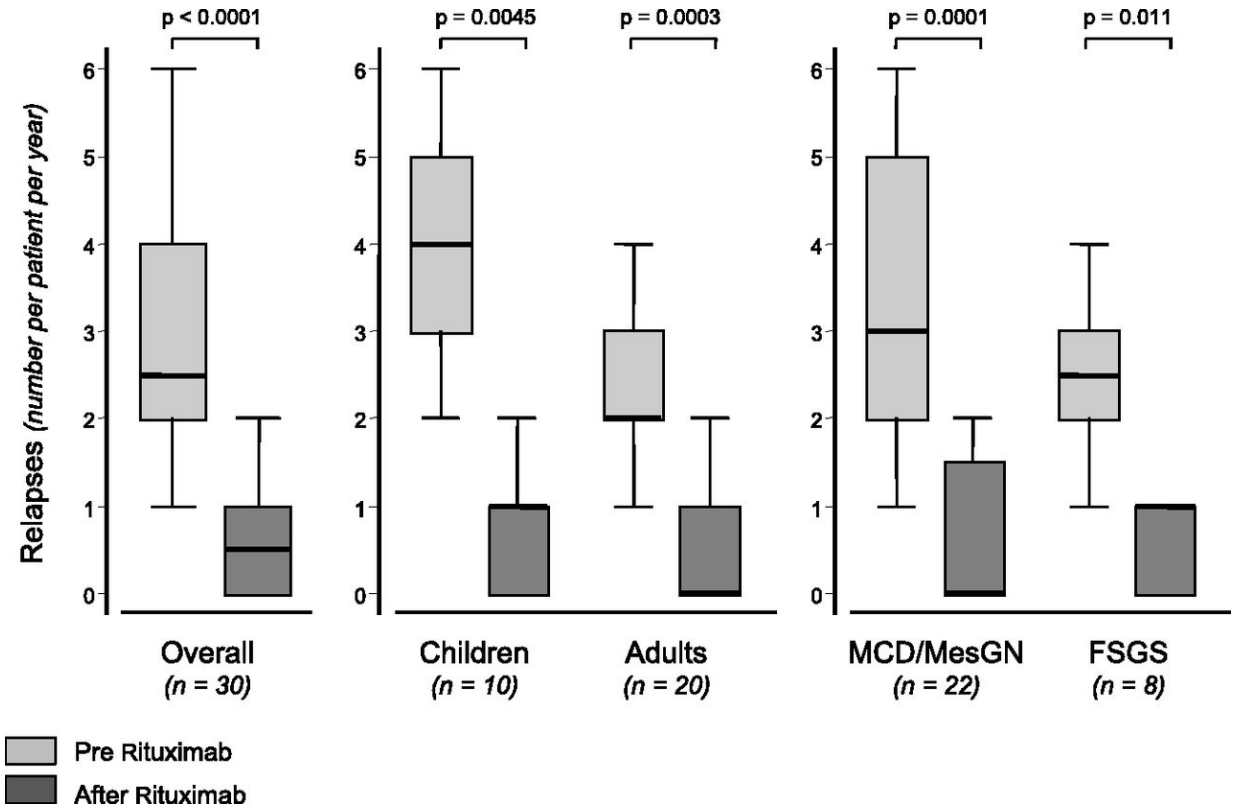
Effect of single-dose RTX on steroid-dependent minimal-change nephrotic syndrome in adults

Parameter	(1st Rituximab)			(2nd Rituximab)		
	Baseline	1 month	3 months	6 months	9 months	12 months
CD19 (/mm^3)	126 ± 134	1.6 ± 1.4$^+$	2.8 ± 6.1$^+$	20 ± 48$^+$	5.3 ± 9.0$^+$	39 ± 137$^+$

- ✓ 3 pts (12%) developed relapse by around 6 months after the first RTX infusion
- ✓ 1 pt (4%) developed relapse by around 6 months after the second RTX infusion
- ✓ All of the pts who developed relapse were revealed to have B-cell repletion.
- ✓ CD19 counts in the pts who developed relapse increased significantly (209 ± 312, 167 ± 229/mm3, P < 0.0001) when compared with that in those who did not develop relapse (18 ± 38, 18 ± 38/mm3) at 6 months after rituximab injection.

Takei T -Nephrology Dialysis Transplantation 2013

Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome



28 pts: single dose of RTX (375 mg/m^2)

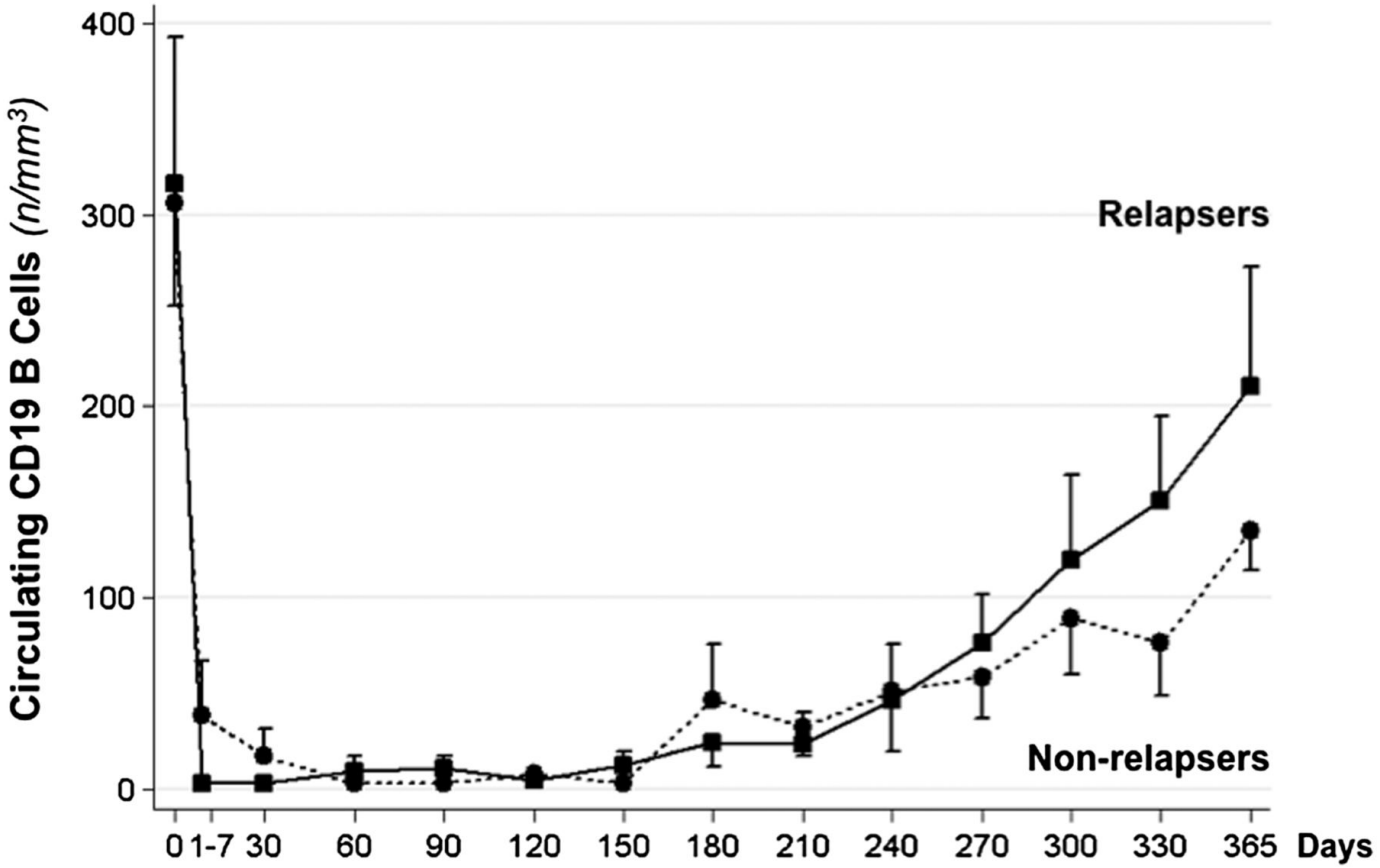
2 pts with increased circulating B cell counts at 1 week received a second dose.

At 1 year, all pts were in remission, 60% of pts were off of all immunosuppressive agents, and 50% never relapsed (9).

Number of NS relapses over 1 year of follow-up after RTX administration, and during the year before rituximab administration in the study group as a whole (overall), and in different age and diagnosis

Ruggenenti et al. JASN 2014;25:850-863

Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome



Circulating B cells at the time of RTX administration (day 0) and at different time points thereafter in participants with or without relapses of NS throughout the 1-year observation period

Ruggenenti et al. JASN 2014;25:850-863

TAKE HOME POINTS

- ✓ MCD is a disease with **complex etiology.**
- ✓ Although the prognosis is generally good, **failure to find a definitive treatment strategy remains a challenge**
- ✓ **Current evidence supports the use of rituximab** in adult MCD also as a front line therapy
- ✓ Serious **adverse effects** of RTX are **uncommon**
- ✓ **Optimal dose of RTX** in adult MCD patients **remains to be established**

Next Webinars

european society for paediatric nephrology

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

era edta WGIKD working group
Working Group on Inherited Kidney Disorders

ERKNet The European Rare Kidney Disease Reference Network

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

Date: **06 Oct 2020**

Speaker: **Olivier Devuyst**

Topic: **Autosomal dominant tubulointerstitial kidney disease**

IPNA Clinical Practice Webinars

Date: **15 Oct 2020**

Speaker: **Louise McAlister and Rukshana Shroff**

Topic**: Dietetic management of calcium-phosphate in children with CKD stage 2-5 and on dialysis - clinical practice recommendations from the pediatric renal nutrition task force**

ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **27 Oct 2020**

Speaker: **Rezan Topaloglu**

Topic: **Classification and physiopathology of vasculitis**

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