Anti-B cell Targeted Therapy in MCD & FSGS

Amir A. Nassiri, M.D, D.I.U

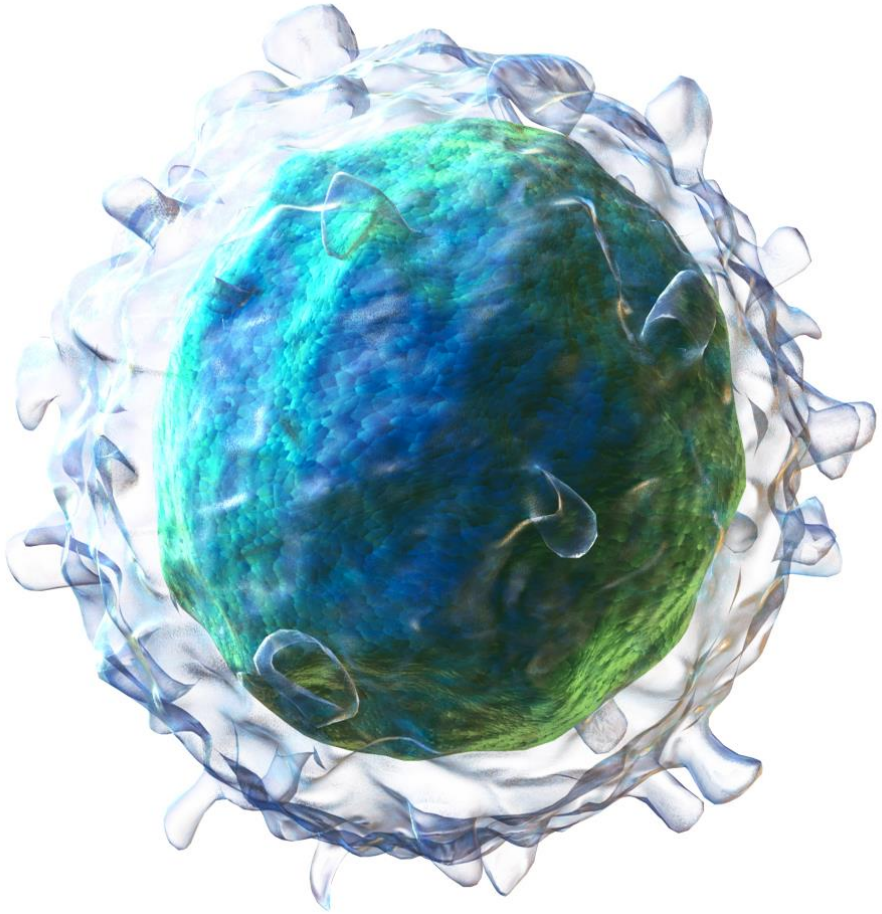
SBUMS

- Substantial **progress** in the field of clinical immunology
- Given the **role of B cells in the pathogenesis of many immunological processes** (Ab & auto-Ab production, T cell regulation, Ag present.), attention >>> focused on the development of mAbs that target B cells.
- ***B cell depletion*** **ttt in auto-immune diseases** >>> clinical ***improvement*** in conditions associated with **Auto-Ab production** >>>
- RA, SLE, ITP, ANCA vasculitis, and immunological mediated kidney diseases such as MCD, FSGS, MGN, CryoGlb, Ab-mediated allograft Rjct,…

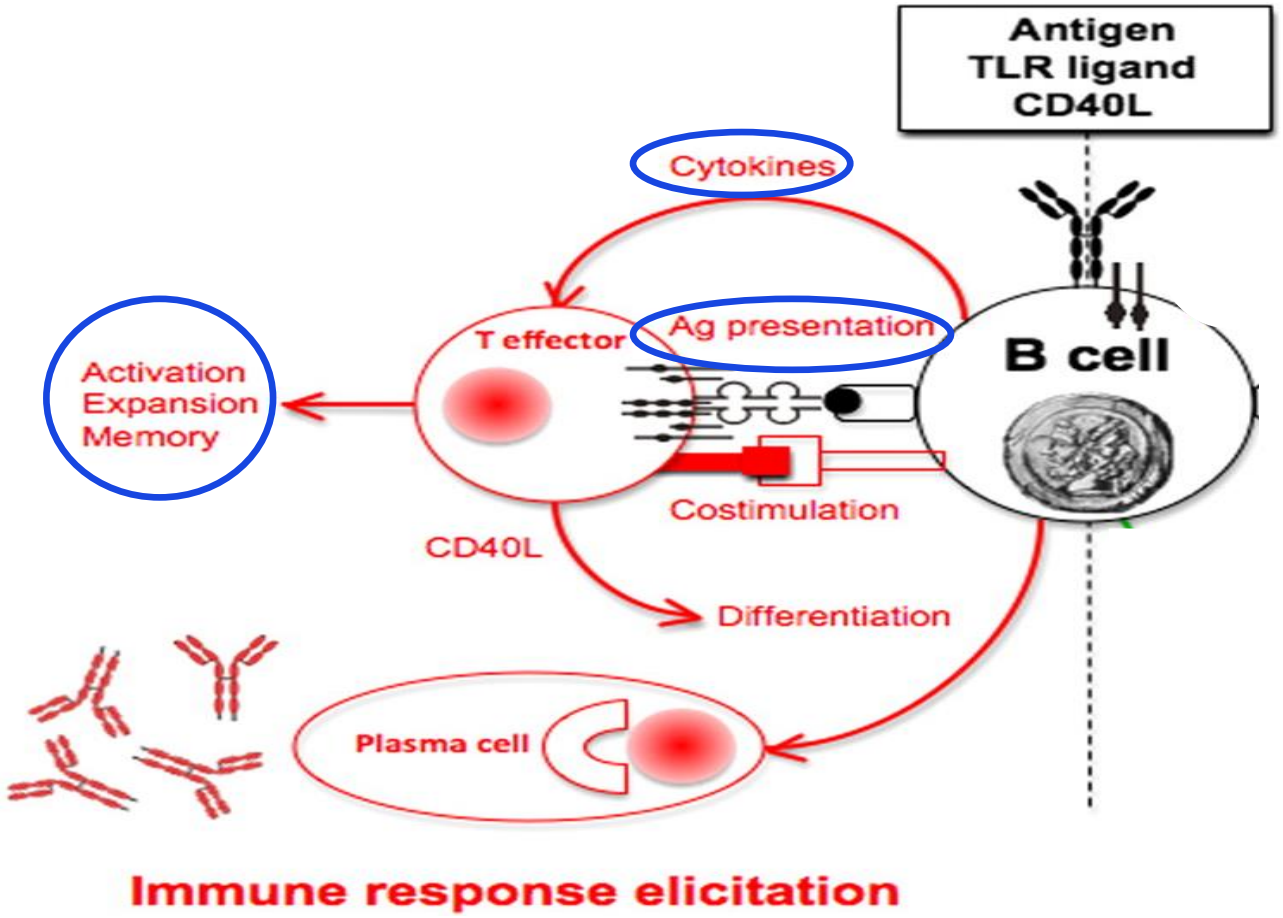
The Importance of B cells

- Recent investigations in nonobese diabetic mice have shown that more than 50% of the lymphocytes infiltrating islets of Langerhans are B cells and that these B cells are critically necessary for the development of diabetes.
- Another clue that **B cells** exert pathogenic roles through "**antibody-independent**" mechanistic pathways came from genetically modified **lupus**-prone mice.
- Although B-cell depletion leads to abrogation of the disease, transgenic mice, whose **B cells cannot secrete immunoglobulin**, still developed **nephritis**.
- Thus, **in many immune diseases**, **even including those not driven by antibodies**, ***B cells have been demonstrated to play an essential pathogenic role.***

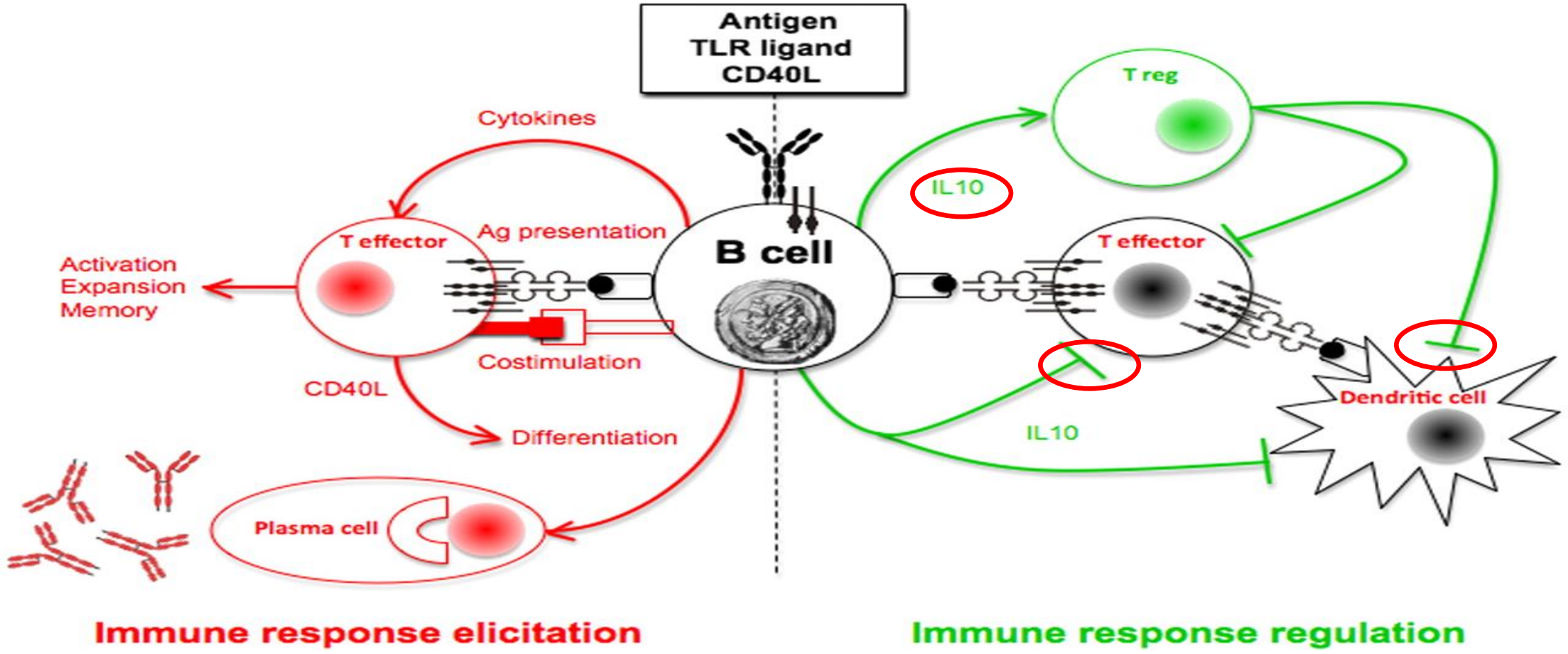
The Janus of the Immune System



start of an (auto)immune process



end of an (auto)immune process



B cell Ambivalent effect on immune system

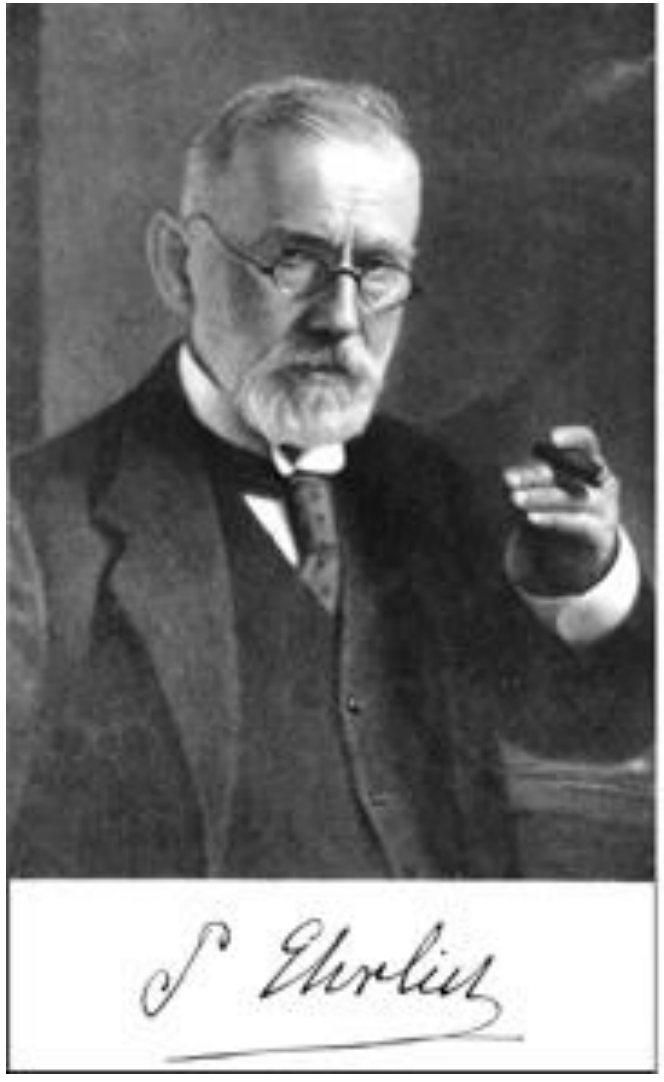
- *CD 20 MAb during the disease progression dramatically reduce the symptoms, BUT the same ttt before, could* ***exacerbate the disease***

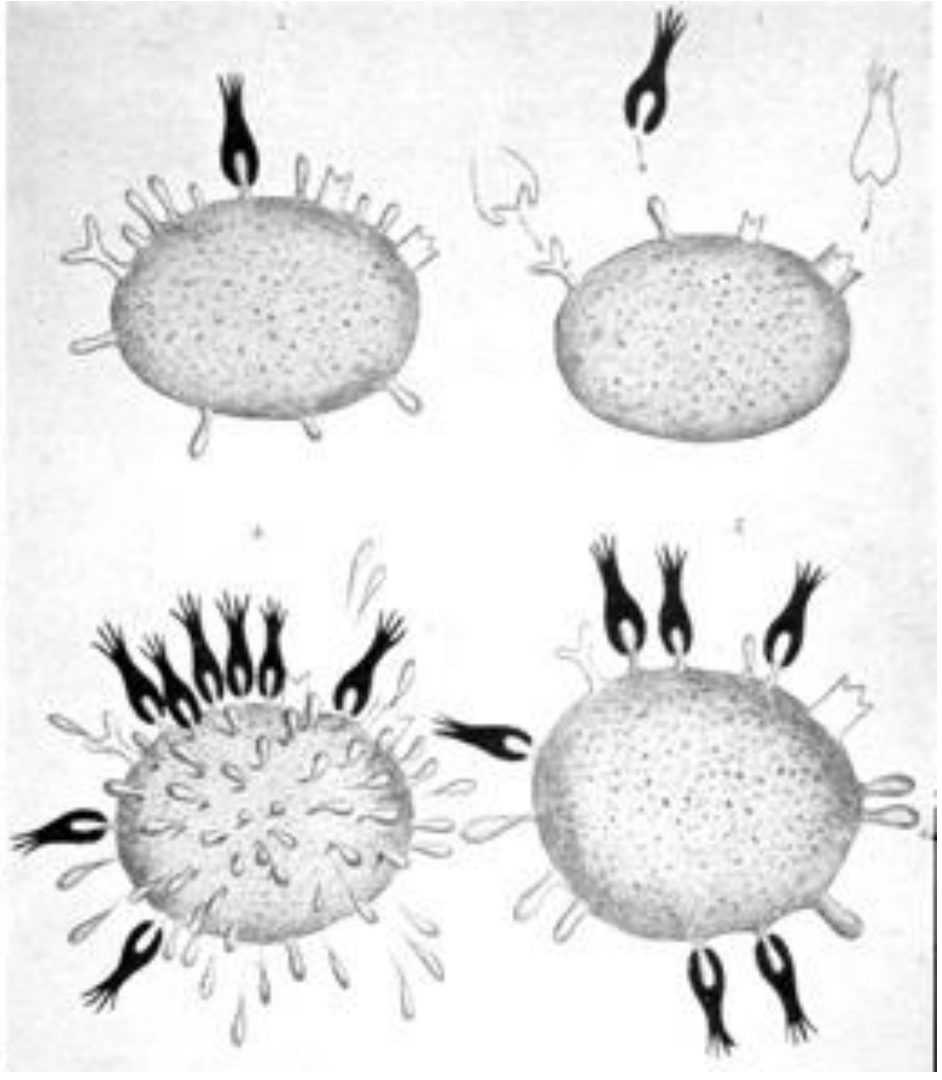
- ***Administrating the drug at some time points had no effect***

- ***The same ttt can lead to opposite outcomes depending on the timing of its administartion***

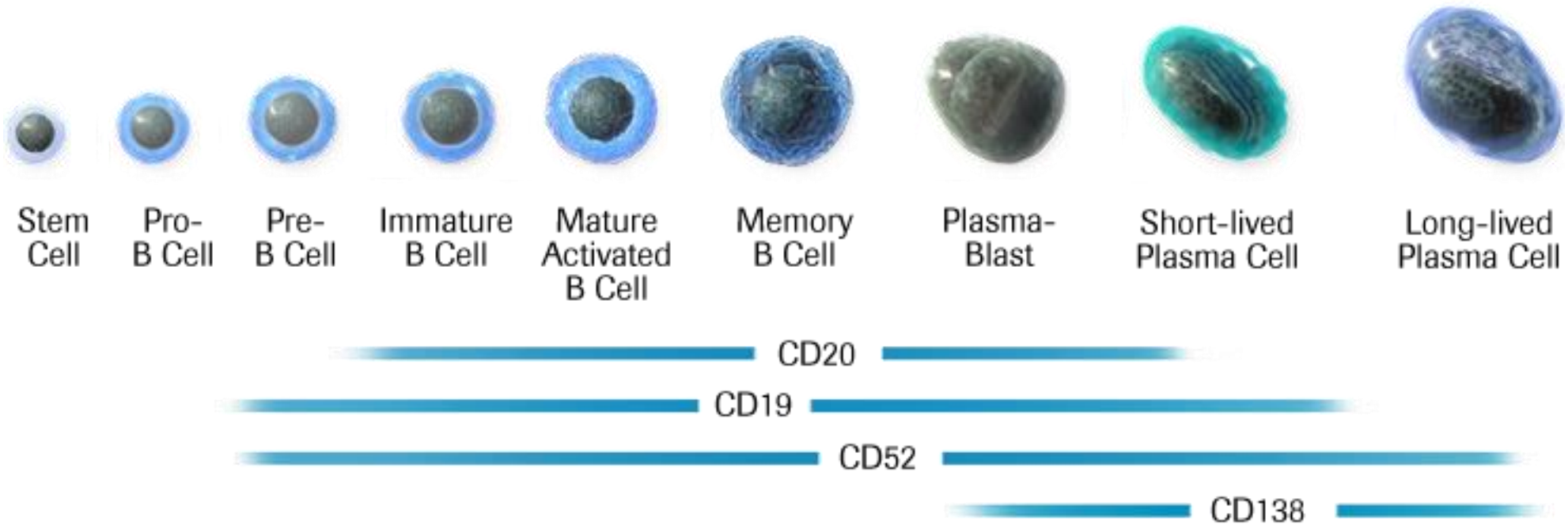
Dr Paul Ehrlich's Magic Bullet theory

"a bullet that destroys pathogens, but not the host"



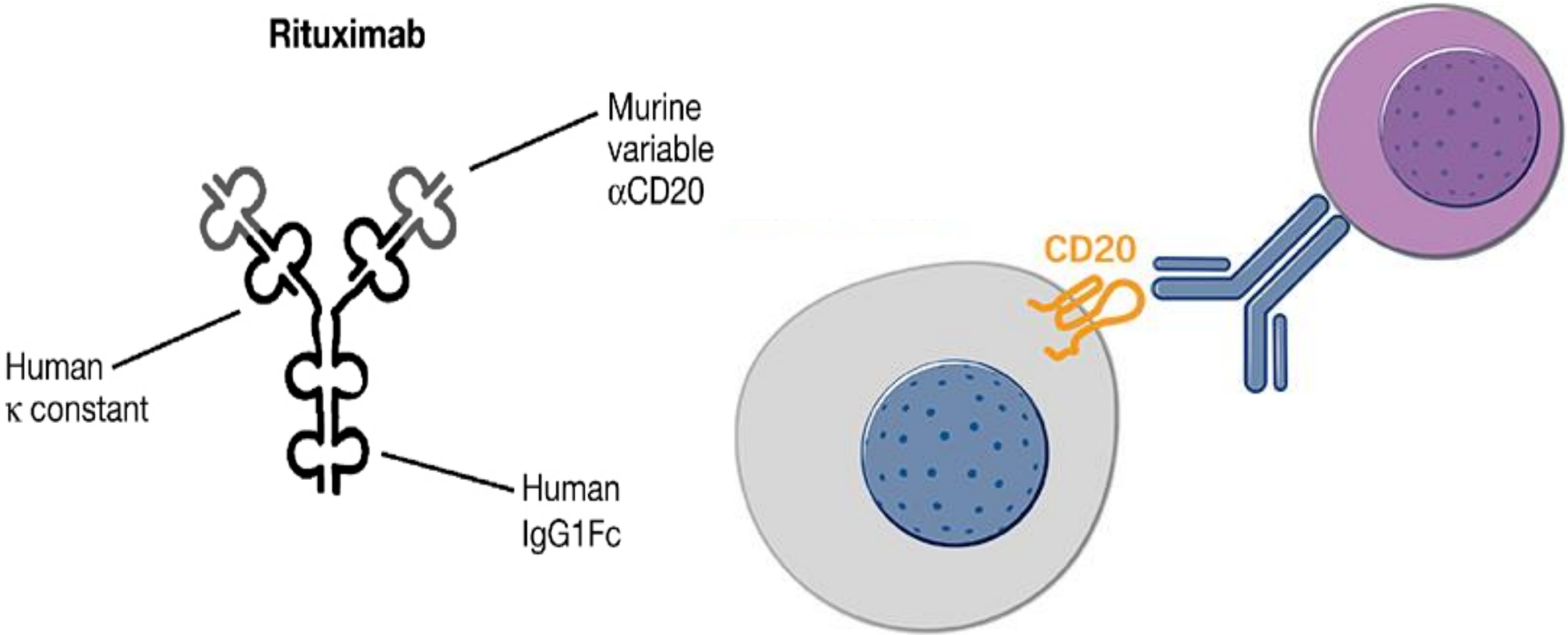


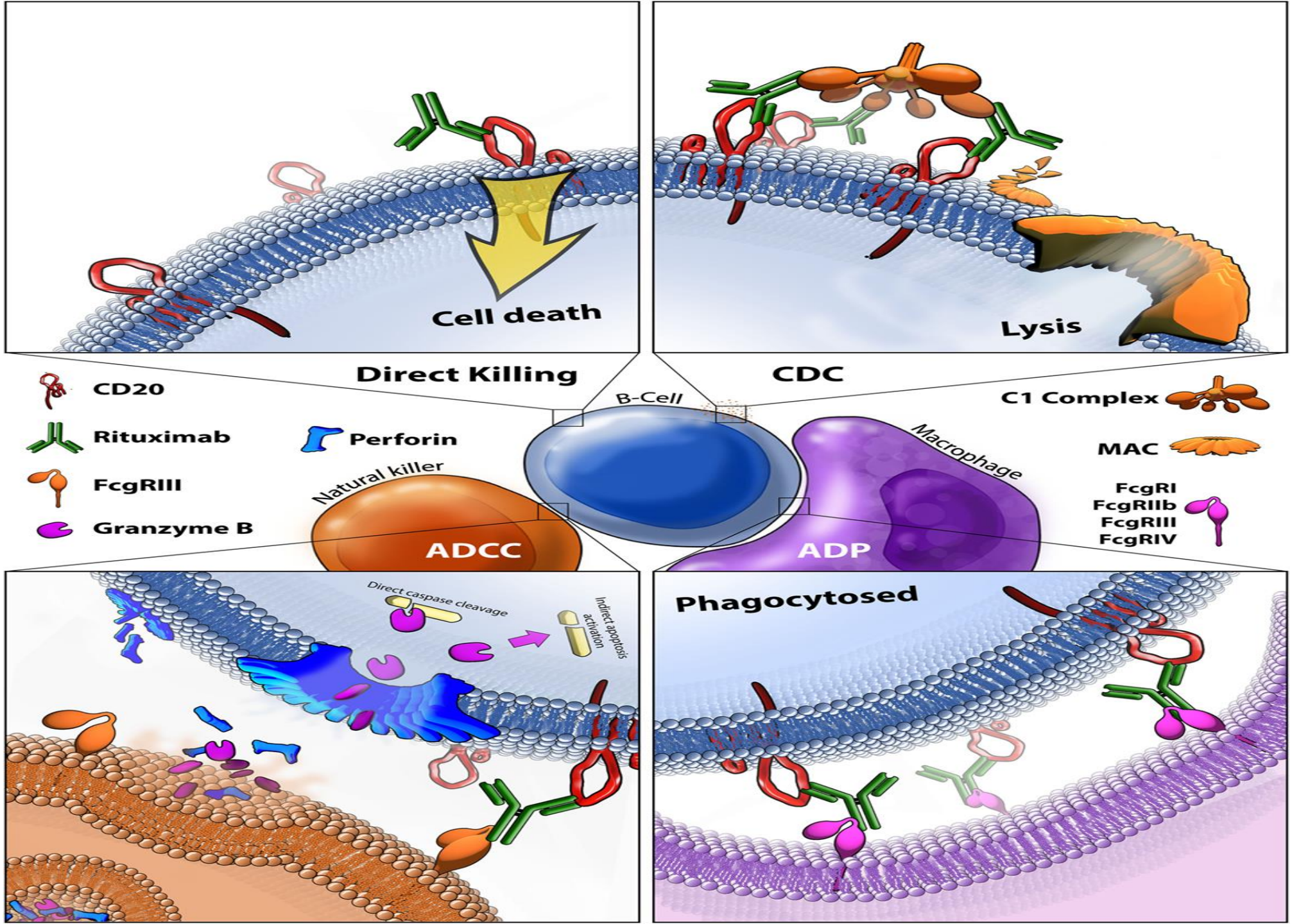
B cell Maturation in Bone Marrow & Peripheral Lymphoid Tissues

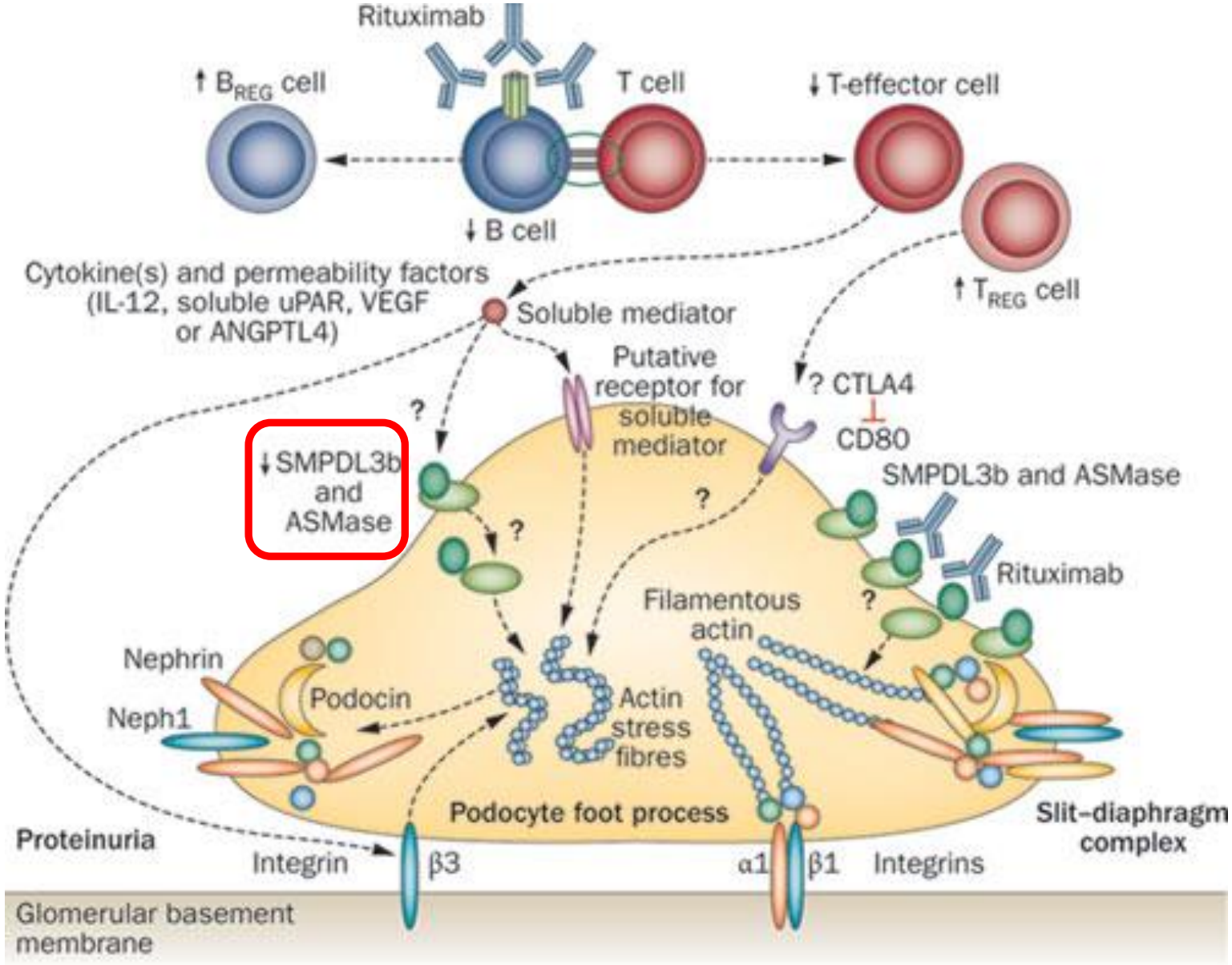


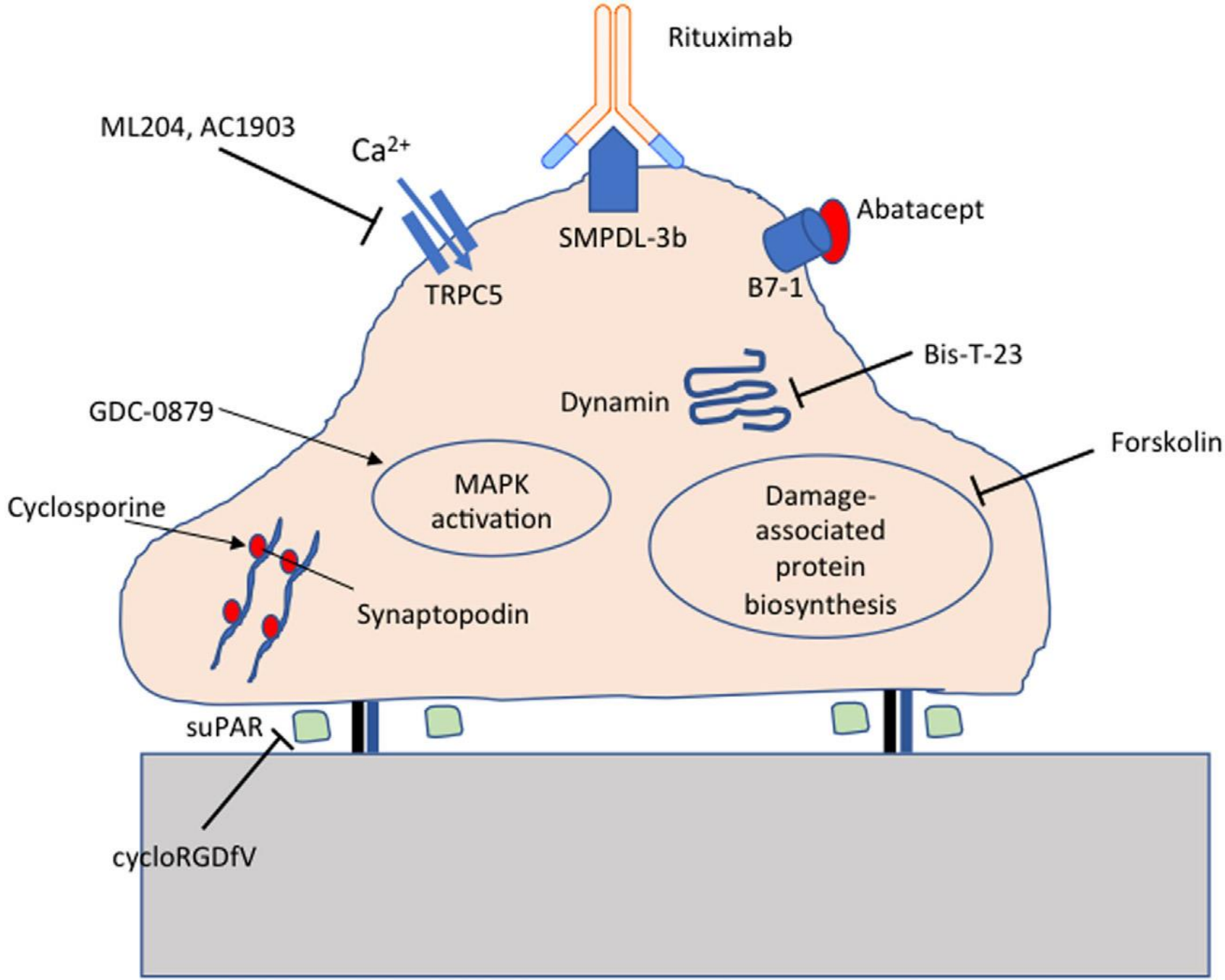
CD20

- CD 20 expressed on the surface of immature & mature B cells but not plasma cells
- **CD 20: mediates proliferation & differentiation of B cells**
- **CD 20 is suspected of acting as a Ca channel in the cell membrane**
- Of the many surface-expressed Ag on B cells CD 20 is ***not shed or modulated*** >> making it **an attractive target**.
- the 1st stage of B cell development does not express CD 20 >>> ***any*** **healthy B cells destroyed by CD 20 ttt can be readily replenished**

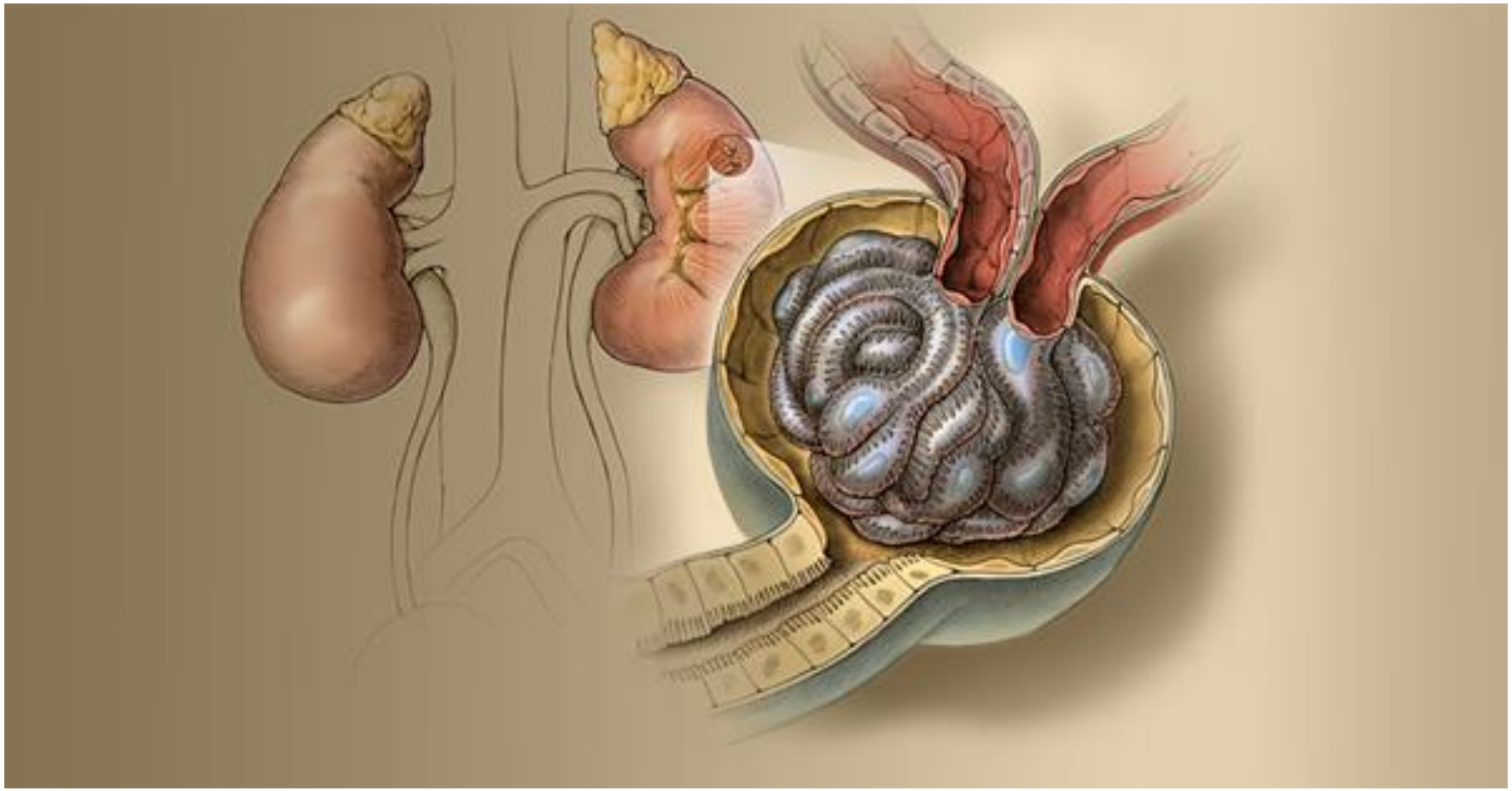

Rituximab
Murine
variable
αCD20
Human
κ constant
Human
IgG1Fc
CD20


Cell death
Lysis
Direct Killing
CDC
CD20
Rituximab
FcgRIII
Granzyme B
Perforin
B-Cell
Natural killer
Macrophage
C1 Complex
MAC
FcgRI
FcgRIIb
FcgRIII
FcgRIV
ADCC
ADP
Direct caspase cleavage
Indirect apoptosis activation
Phagocytosed


Rituximab
↑ B_{REG} cell
T cell
↓ T-effector cell
↓ B cell
↑ T_{REG} cell
Cytokine(s) and permeability factors (IL-12, soluble uPAR, VEGF or ANGPTL4)
Soluble mediator
Putative receptor for soluble mediator
? CTLA4
CD80
↓ SMPDL3b and ASMase
SMPDL3b and ASMase
Rituximab
Filamentous actin
Nephrin
Podocin
Neph1
Actin stress fibres
Podocyte foot process
Slit–diaphragm complex
Proteinuria
Integrin
β3
α1
β1
Integrins
Glomerular basement membrane


Rituximab
ML204, AC1903
Ca2+
SMPDL-3b
Abatacept
TRPC5
B7-1
Bis-T-23
Dynamin
GDC-0879
Forskolin
MAPK activation
Damage-associated protein biosynthesis
Cyclosporine
Synaptopodin
suPAR
cycloRGDfV

RTX in Glomerular Diseases



RTX in Glomerular Diseases

- B Cell ttt >>> increasingly used in pts with iNS, such as iMGN, MCD, iFSGS
- The most investigated B cell targeted ttt in primary GN >>> RTX
- Suggested that >>> RTX is equivalent to Std IS ttt in SD-MCD/ SD-FSGS
- No proof of efficacy in SR diseases.

MCD/FSGS

- Given the similar clinical presentation in minimal-change disease (MCD) and FSGS, it was not until the mid-20th century that it was reported there was a **different clinical course** for patients with NS in those with minimal glomerular changes versus those with juxtamedullary glomerular hyaline or sclerosing glomerular lesions without cellular proliferation.
- The relationship straining be- tween the 2 pathology morphologies, MCD and FSGS— initially often considered as part of the same spectrum— were separated into unique clinicopathologic entities following a histopathologic classification of nephrotic syn- drome for the International Study of Kidney Disease in Children.

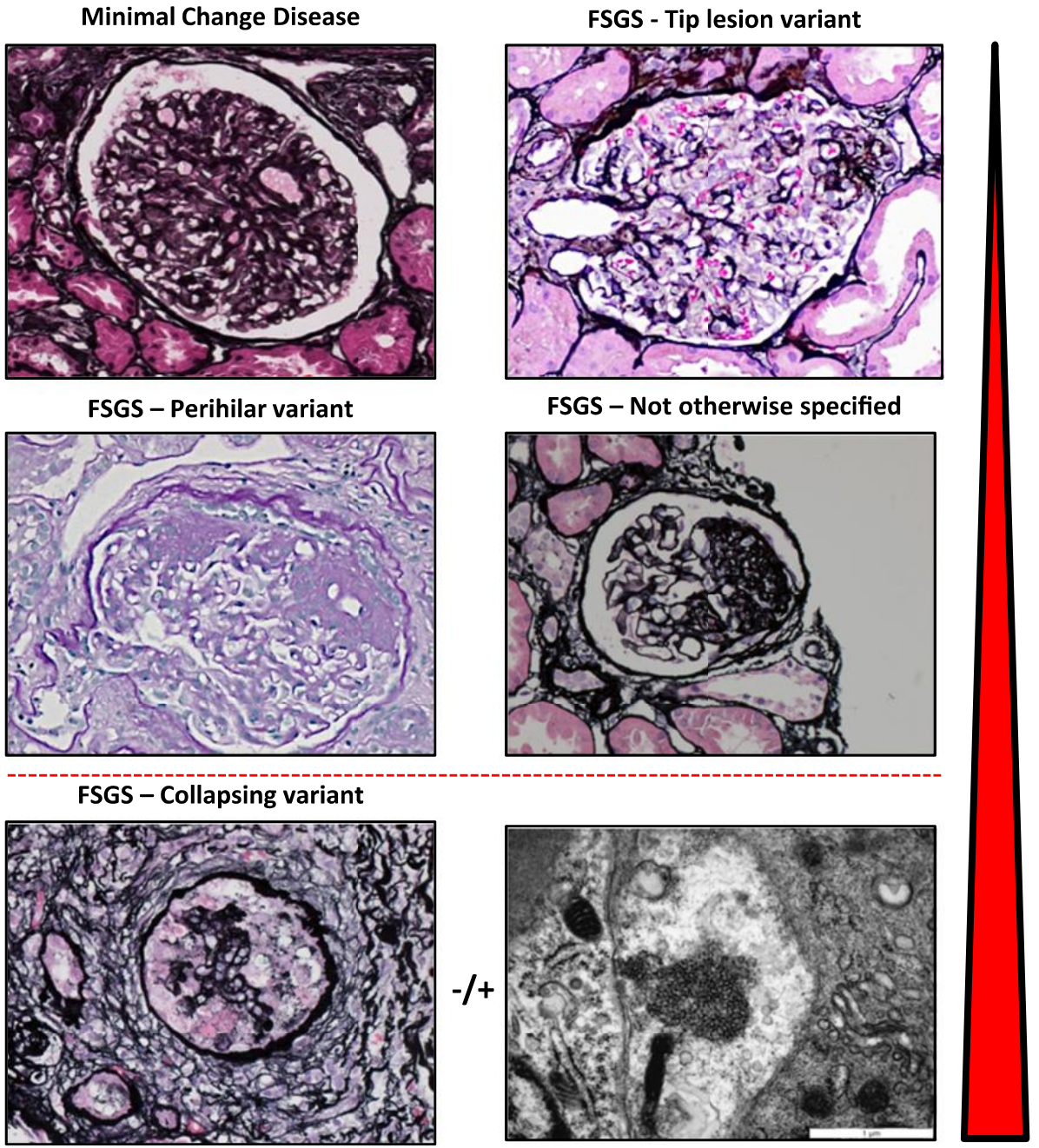
PERSPECTIVES

OPINION

Minimal change disease and idiopathic FSGS: manifestations of the same disease

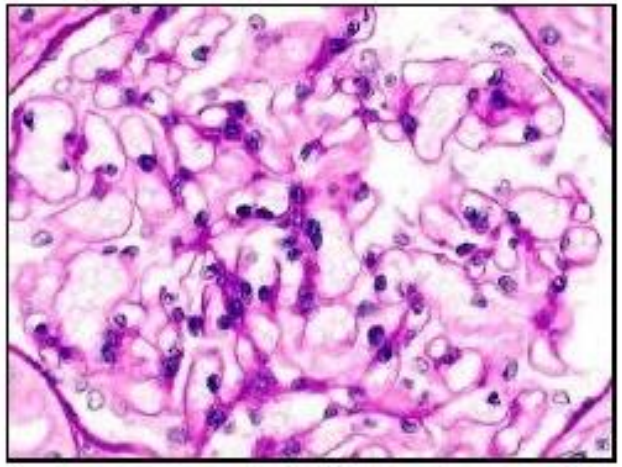
Rutger J. Maas[1], Jeroen K. Deegens[1], Bart Smeets[2], Marcus J. Moeller[3] and Jack F. Wetzels[1]

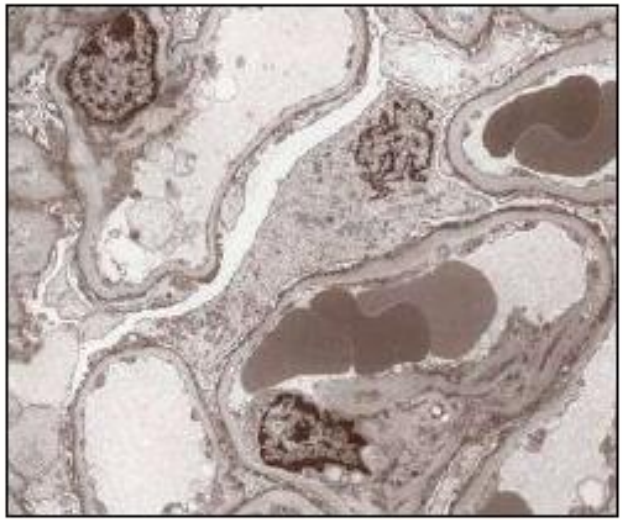
Abstract | Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the key histological findings in patients with idiopathic nephrotic syndrome (INS). Although MCD and idiopathic FSGS are often considered to represent separate entities based on differences in their presenting characteristics, histology and outcomes, little evidence exists for this separation. We propose that MCD and idiopathic FSGS are different manifestations of the same progressive disease. The gradual development of FSGS in patients with non-remitting or relapsing INS has been well documented. Moreover, FSGS is the uniform result of substantial podocyte loss in animal models, and a common feature of virtually all progressive human glomerulopathies. As evidence suggests a common aetiology, the pathogenesis of MCD and idiopathic FSGS should be studied together. In clinical trials, idiopathic FSGS should be considered to represent an advanced stage of disease progression that is less likely to respond to treatment than the earlier stage of disease, which is usually defined as MCD.



MCD

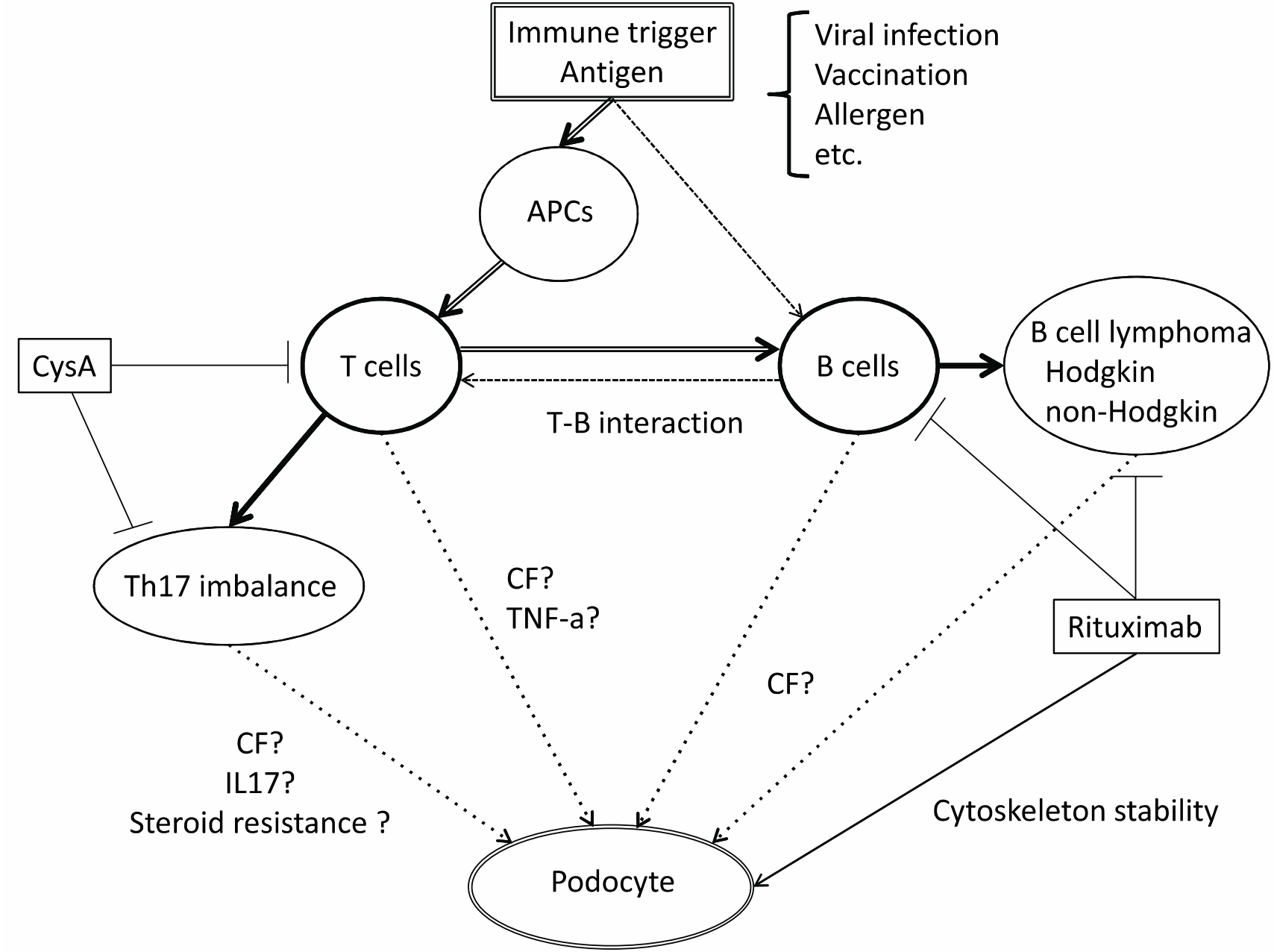
Synonyms:	**Nil disease, lipoid nephrosis, foot process disease**
Incidence:	**80% of nephrotic syndrome in children (1-8 yrs.), mostly male. Adults in 2nd-3rd decade.**
Etiology:	**Idiopathic. Loss of net negative charge destruction of podocyte foot processes.**
Clinical Features:	**Nephrotic syndrome. History of recent URI in 30%. Association with Hodgkin's lymphoma. Overlap with FSGS patients.**
Lab Features:	**Nephrotic urine (polyuria, Selective proteinuria. (albuminuria).**
Pathology:	**LM - Normal. IF - Negative. EM - Focal fusion/loss of foot processes.**
Clinical Course:	**Spontaneous remission in 25-40%. Complete remission in 65-70% of patients. Steroid resistant patients may progress to FSGS.**





MCD

- Most will respond to Steroid, but up to 1/3 become SD, or FR
- SR or SD >>> a major problem in the ttt course
- MCD >>> result from a “circulating T-cell factor” that cause podocyte cytoskeleton dis-organization
- Historically >>> MCD has been considered a T-cell pathology


Immune trigger
Antigen
Viral infection
Vaccination
Allergen
etc.
APCs
CysA
T cells
B cells
B cell lymphoma
Hodgkin
non-Hodgkin
T-B interaction
Th17 imbalance
CF?
TNF-a?
CF?
Rituximab
CF?
IL17?
Steroid resistance ?
Cytoskeleton stability
Podocyte

Unexpected Efficacy of Rituximab in Multirelapsing Minimal Change Nephrotic Syndrome in the Adult: First Case Report and Pathophysiological Considerations

Hélène François, MD, PhD, Eric Daugas, MD, PhD, Albert Bensman, MD, and Pierre Ronco, MD, PhD

Nephrotic syndrome secondary to minimal change disease (MCNS) usually is considered to have a good renal prognosis, but frequency of relapses and steroid dependency are therapeutic challenges to physicians. Treatment of patients with multiple relapses remains controversial because few control studies are available. We report the case of a 23-year-old woman of Malian origin who experienced more than 30 relapses of MCNS. Long-term remission was observed only with rituximab (anti-CD20 antibody) treatment after step-by-step use of all currently available medications for MCNS were unsuccessful. Our observation is the first report of efficacy of rituximab during multirelapsing MCNS in an adult patient with a significant follow-up and no adjuvant therapy. This case suggests a role of B cells in MCNS, possibly by regulating T-cell function.
Am J Kidney Dis 49:158-161.

INDEX WORDS: Minimal change disease; multirelapsing nephrotic syndrome; rituximab.

the 1st case report

- 1st case that reported the use of RTX in the management of MCD in adults >>> 2007 (Francois H et al, Unexpected efficacy of RTX in multirelapsing MCD in the adult: the first case report, Am J Kidney Dis, 2007)
- 23 y/o women, >30 relapse since 6 yrs, failure to respond to all other potentially steroid-sparing drugs (CPA, CsA, MMF) + CNI Toxicity, HTN
- 4 w RTX >>> long-term remission 3 w after ttt >>> still at 28 mo !

Netherlands
The Journal of Medicine

REVIEW

Rituximab in minimal change nephropathy and focal segmental glomerulosclerosis: report of four cases and review of the literature

H.P.E. Peters[1*], N.C.A.J. van de Kar[2], J.F.M. Wetzels[1]

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http://www.kidney-international.org

clinical trial

see commentary on page 343

Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease

Helene Munyentwali[1,8], Khedidja Bouachi[2,3,8], Vincent Audard[2,3,4], Philippe Remy[2,3], Philippe Lang[2,3,4], Rachid Mojaat[1], Georges Deschênes[5], Pierre M. Ronco[1,6,7], Emmanuelle M. Plaisier[1,6,7,8] and Karine Y. Dahan[1,8]

- 17 pts SD/FR despite several IS >>> RTX,
- different protocol between pts !, some pts received 2 nd course of RTX, during F/U CD19 recovery
- RTX >>> sustained remission with NO relapse in 65% for 2 yrs
- No MAE

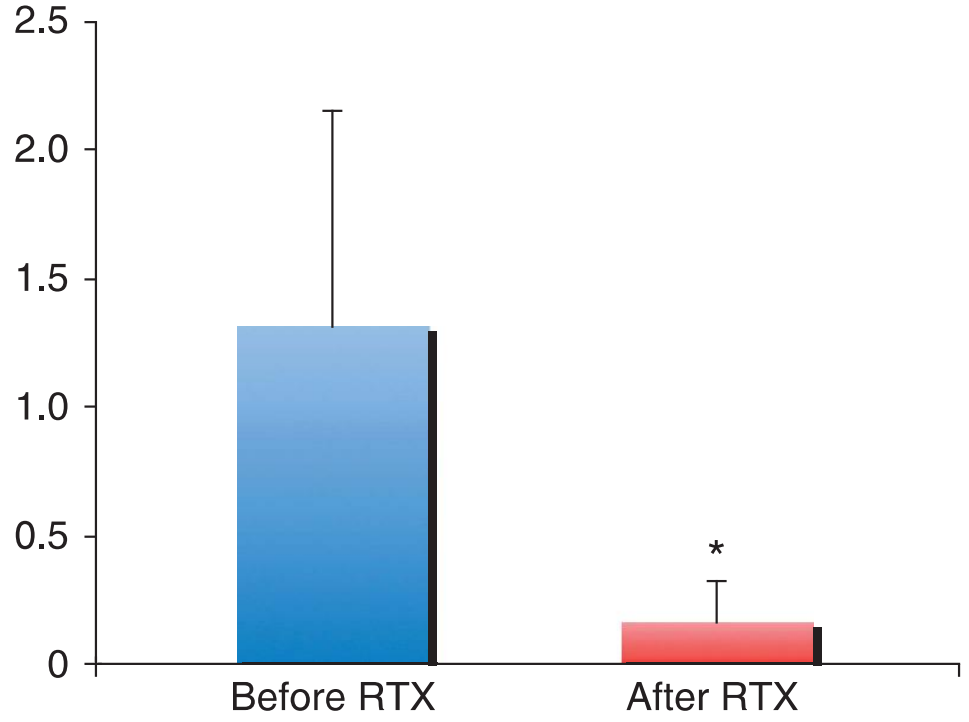

Figure 1 | Number of relapses per year before and after rituximab treatment (*$P < 0.05$). Results are the mean ± s.d.

Nephrol Dial Transplant (2014) 0: 1–8
doi: 10.1093/ndt/gfu209

ndt
Nephrology Dialysis Transplantation

Original Article

Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance

Joëlle Guitard[1,†], Anne-Laure Hebral[1,†], Fadi Fakhouri[2], Dominique Joly[3], Eric Daugas[4], Joseph Rivalan[5], Vincent Guigonis[6], Françis Ducret[7], Claire Presne[8], Yves Pirson[9], Maryvonne Hourmant[2], Jean-Claude Glachant[10], Benoit Vendrely[11], Olivier Moranne[12], Stanislas Faguer[1,†] and Dominique Chauveau[1,†]

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[†]These authors contributed equally to this work.

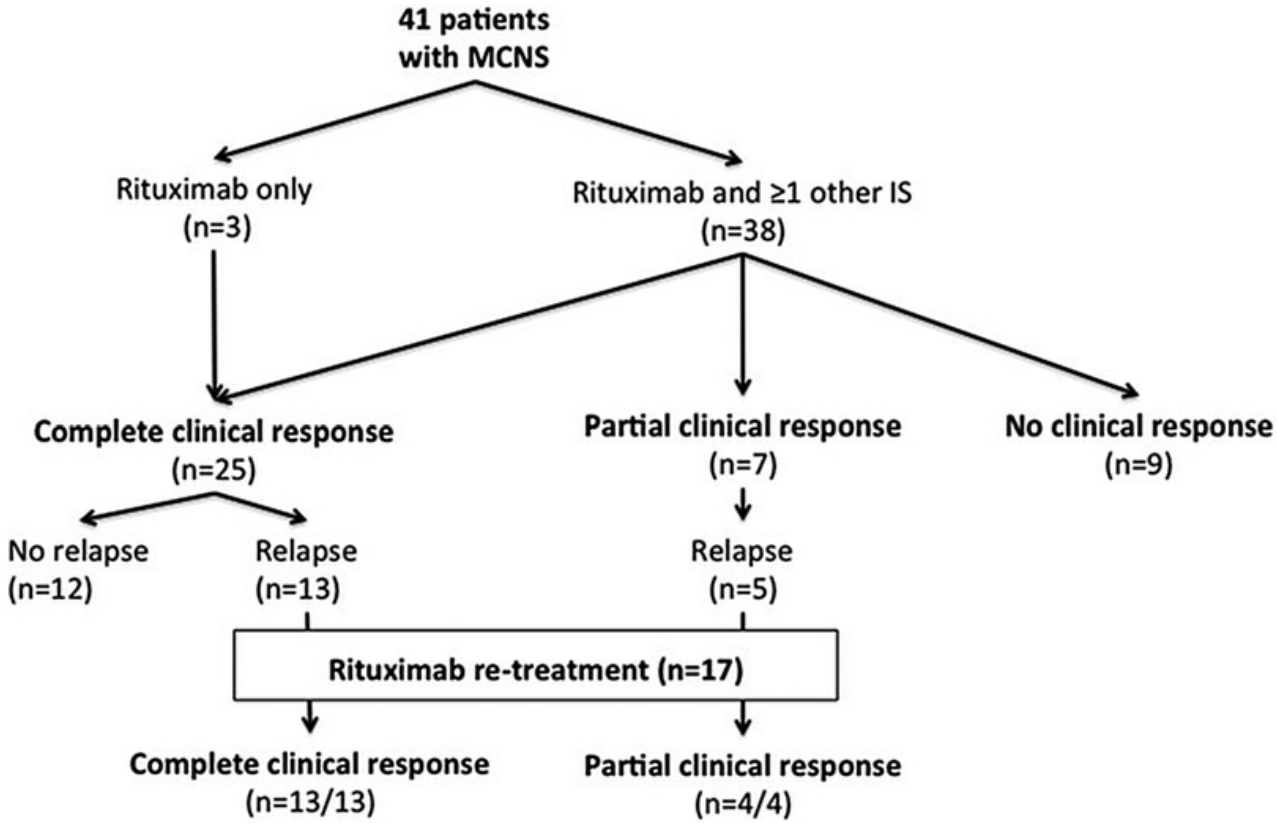
ABSTRACT

Background. Minimal-change nephrotic syndrome (MCNS) is a common cause of steroid sensitive nephrotic syndrome (NS) with frequent relapse. Although steroids and calcineurin inhibitors (CNIs) are the cornerstone treatments, the use of rituximab (RTX), a monoclonal antibody targeting B cells, is an efficient and safe alternative in childhood.
Methods. Because data from adults remain sparse, we conducted a large retrospective and multicentric study that included 41 adults with MCNS and receiving RTX.
Results. Complete (NS remission and withdrawal of all immunosuppressants) and partial (NS remission and withdrawal of at least one immunosuppressants) clinical responses were obtained for 25 and 7 patients, respectively (overall response 78%), including 3 patients that only received RTX and had a complete clinical response. After a follow-up time of 39 months (6–71), relapses occurred in 18 responder patients [56%, median time 18 months (3–36)]. Seventeen of these received a second course of RTX and then had a complete ($n = 13$) or partial ($n = 4$) clinical response. From multivariate analysis, on-going mycophenolate mofetil (MMF) therapy at the time of RTX was the only predictive factor for RTX failure [HR = 0.07 95% CI (0.01–0.04), P = 0.003]. Interestingly, nine patients were still in remission at 14 months (3–36) after B-cell recovery. No significant early or late adverse event occurred after RTX therapy.
Conclusions. RTX is safe and effective in adult patients with MCNS and could be an alternative to steroids or CNIs in patients with a long history of relapsing MCNS.

Keywords: B-cells, minimal-change disease, nephrotic syndrome, rituximab, steroids

INTRODUCTION

Minimal-change nephrotic syndrome (MCNS) is the most frequent cause of acquired glomerular disease in children, and accounts for 20% of nephrotic syndromes (NS) in adulthood. MCNS results from a loss of the cytoskeleton organization at



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doi: 10.1093/ndt/gfs515
Advance Access publication 13 December 2012

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

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Keywords: nephrotic syndrome, relapse, rituximab, steroid dependent minimal-change

ORIGINAL ARTICLE

ABSTRACT

Background. Steroid-dependent minimal-change nephrotic syndrome (MCNS) requires administration of prolonged courses of prednisolone (PSL); therefore, a paradigm shift from such toxic 'non-specific' therapies to selective immunomodulating regimens is necessary for these cases.
Methods. To assess the therapeutic effects of rituximab (an anti-CD20 antibody) in adult patients with steroid-dependent MCNS, we performed a prospective trial of the effects of a single dose of rituximab administered twice at an interval of 6 months in 25 MCNS patients. We evaluated the biochemical parameters and compared the clinical findings between the 12-month period before and 12-month period after the first rituximab infusion.
Results. A significant reduction in the number of relapses and the total dose and the maintenance dose of PSL administered was observed during the 12-month period after the first rituximab infusion when compared with the findings during the 12-month period before the first rituximab infusion [25 (100%) versus 4 (16%), $P < 0.001$; 8.2 versus 3.3 g, $P < 0.001$; 26.4 mg/day at baseline versus 1.1 mg/day at 12-month, $P < 0.0001$]. Complete remission was achieved/maintained in all patients undergoing B-cell depletion. Four of 17 patients with B-cell repletion developed relapse.
Conclusions. Our results revealed that rituximab therapy was associated with a reduction in the number of relapses and in the total dose of PSL needed. Therefore, rituximab appears to be a useful therapeutic agent for adult patients with steroid-dependent MCNS. These results suggest that this treatment is rational and should be considered as an important option in the management of adult patients with steroid-dependent MCNS.

INTRODUCTION

Patients with steroid-dependent minimal-change nephrotic syndrome (MCNS) are usually treated with steroids and

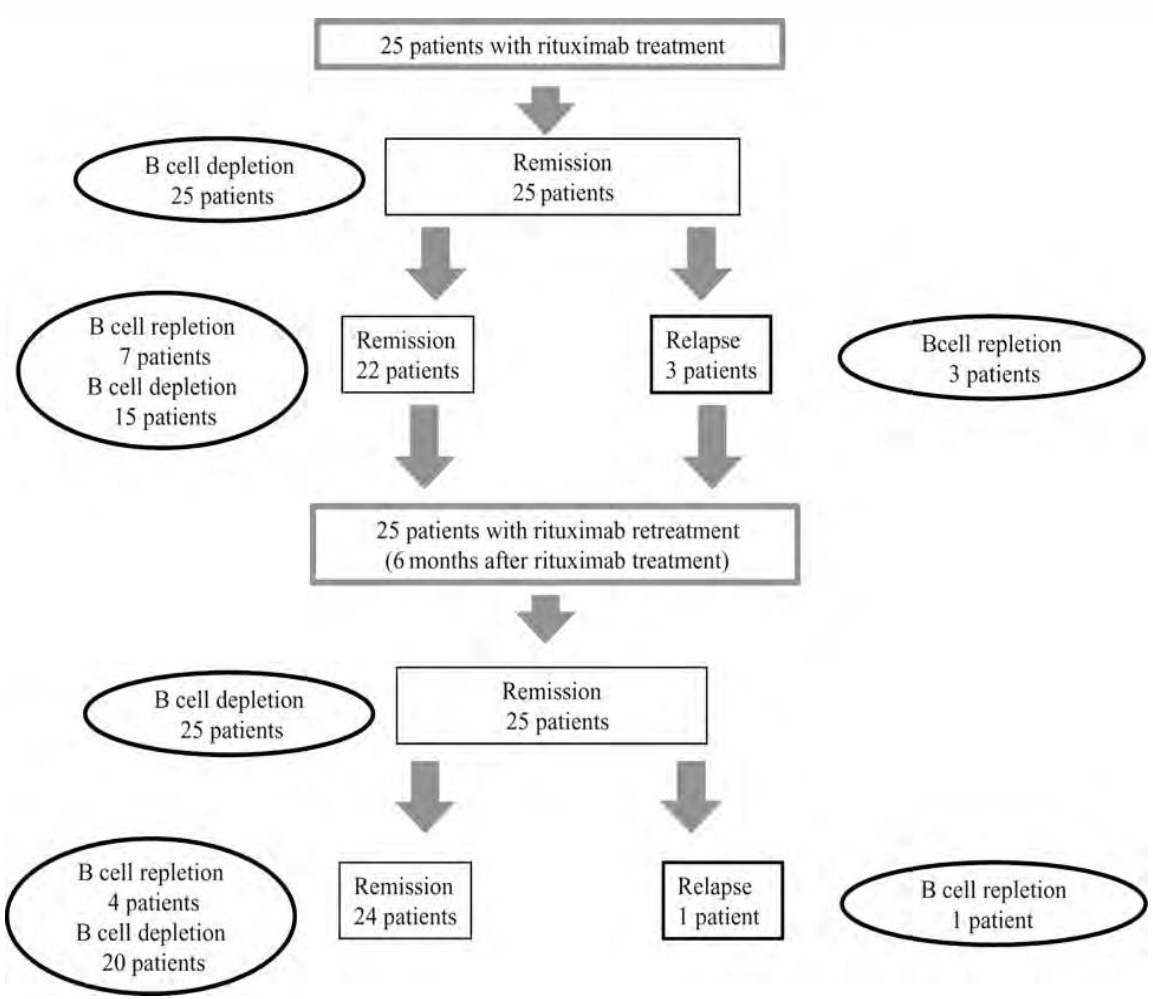

FIGURE 2: Clinical follow-up after rituximab treatment.

OPEN

Long-Term Prognosis of Adult Patients with Steroid-Dependent Minimal Change Nephrotic Syndrome Following Rituximab Treatment

Yuko Iwabuchi, MD, Takashi Takei, MD, PhD, Takahito Moriyama, MD, PhD, Mitsuyo Itabashi, MD, PhD, and Kosaku Nitta, MD, PhD

Abstract: This study was to evaluate the long-term efficacy and safety of a single-dose rituximab regimen rituximab treatment in adult patients with steroid-dependent minimal change nephrotic syndrome (MCNS).

We conducted a prospective cohort study with historical controls to evaluate the effect of single-dose infusions of rituximab at 375 mg/m^2 BSA per dose administered at intervals of 6 months for a period of 24 months. At the end of the 24-month period, the patients were divided into the treatment continuation (n = 20) and treatment discontinuation (n = 5) groups according to their intention to continue/discontinue the treatment.

A significant reduction in the total number of relapses was observed during the 24-month period after the first rituximab infusion as compared with that during the 24-month period before the first rituximab infusion (108 vs. 8, $P < 0.001$). Complete remission was induced/maintained in all patients from 12 to 24 months after the first rituximab infusion. In regard to the clinical course after 24 months, 4 of the 20 patients in the treatment continuation group discontinued the rituximab treatment after the fifth infusion and 2 patients discontinued the treatment after the sixth infusion. However, complete remission was maintained in all the 20 patients of this group during the 12-month observation period after the first four single-dose rituximab infusions. On the other hand, 1 of the 5 patients in the treatment discontinuation group developed relapse during the observation period after the first four rituximab infusions, and the rituximab treatment was resumed.

In our trial, rituximab therapy was associated with maintenance of complete remission. Complete remission was maintained even in most of the patients who showed B-cell repletion after discontinuation of rituximab therapy. Thus, rituximab may be considered as a radical therapeutic agent for patients with steroid-dependent MCNS.

(*Medicine* 93(29):e300)

Abbreviations: CyA = cyclosporine, CYC = cyclophosphamide, MCNS = minimal change nephrotic syndrome, MMF = mycophenolate mofetil, MZ = mizoribine, RRED = prednisolone, TAC = tacrolimus.

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The authors declare that no conflict of interest exist.

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INTRODUCTION

Steroid-dependent minimal change nephrotic syndrome (MCNS) necessitates the administration of prolonged courses of treatment with prednisolone (PRED). Therefore, most of these patients require the addition of another immunosuppressive drug(s), such as cyclosporine (CyA), tacrolimus (TAC), mycophenolate mofetil (MMF), cyclophosphamide (CYC) or mizoribine (MZ), to reduce the number of relapses and prevent the major side effects of steroid treatment.[1] However, these immunosuppressive medications may be unable to induce remission and may also have significant adverse effects of their own.[2,3] Recently, a number of publications have reported the usefulness of rituximab for the treatment of MCNS in pediatric patients,[4–13] while there are fewer reports, including our previous reports, of treatment in the adult setting.[14] The rituximab doses used for the treatment of steroid-dependent MCNS in these studies vary greatly, from a single flat dose of 500 or 1000 mg at 1 or 2 time-points, to 375 mg/m^2 BSA once weekly for 4 weeks. It is difficult to draw any robust conclusions about the optimal dosing schedule of rituximab from these previous reports.

We published the results of a prospective trial of the effects of a single dose of rituximab administered twice at an interval of 6 months in 25 steroid-dependent MCNS patients.[14] Herein, we report the results of our prospective study carried out to examine the long-term efficacy and safety of single-dose administrations of rituximab at intervals of 6 months for a period 24-months, and also the clinical courses of the patients after the rituximab treatment for 24 months in patients with steroid-dependent MCNS.

METHODS

Patient Population

Patients fulfilling the following criteria were enrolled in this study: Patients with steroid-dependent nephrotic syndrome, defined as the occurrence of relapse during the tapering down or within 2 weeks of discontinuation of PRED. Nephrotic syndrome was defined as urinary protein excretion of ≥3.5 g/day, serum albumin of <3.0 g/dL, edema, and hyperlipidemia. Relapse was defined as recurrence of massive proteinuria (daily urinary protein excretion of ≥3.5 g/day or 3+ or 4+ result of the urine albumin dipstick test for albumin); biopsy-proven diagnosis of minimal-change disease; no known associated systemic disease, including negative serology for hepatitis B and C, HIV and antinuclear antibodies, and no positive family history; no

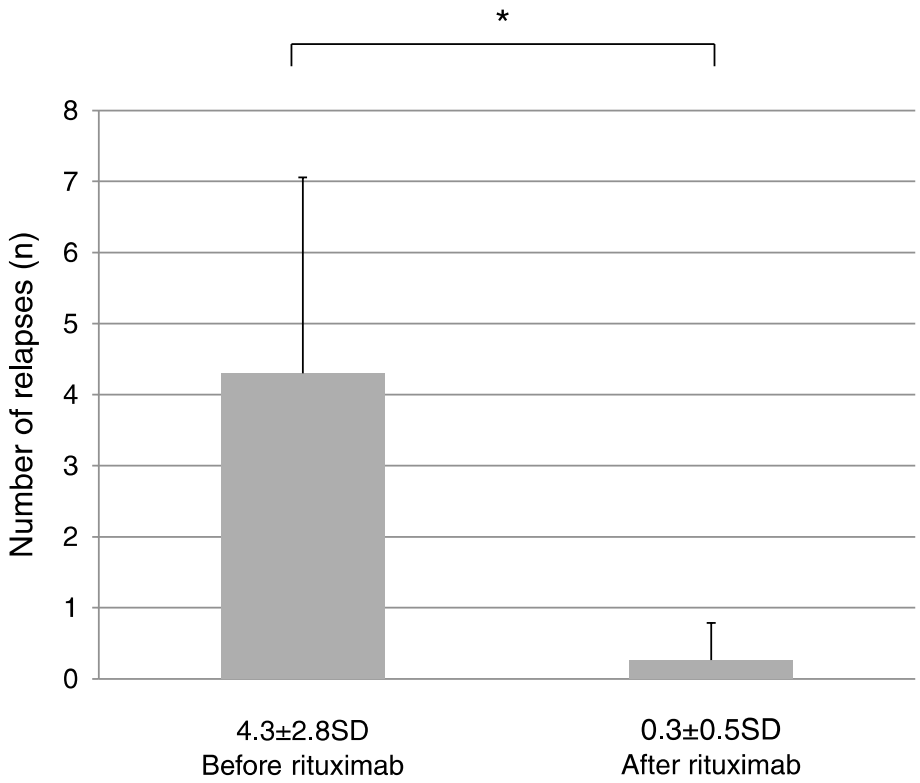

FIGURE 2. Number of relapses during the 24-month period before and 24-month period after the 1st rituximab administration. Results are expressed as means ± S.D. $*P < 0.05$.

Review

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Rituximab in Adult Minimal Change Disease and Focal Segmental Glomerulosclerosis

Andreas Kronbichler[a] Annette Bruchfeld[b]

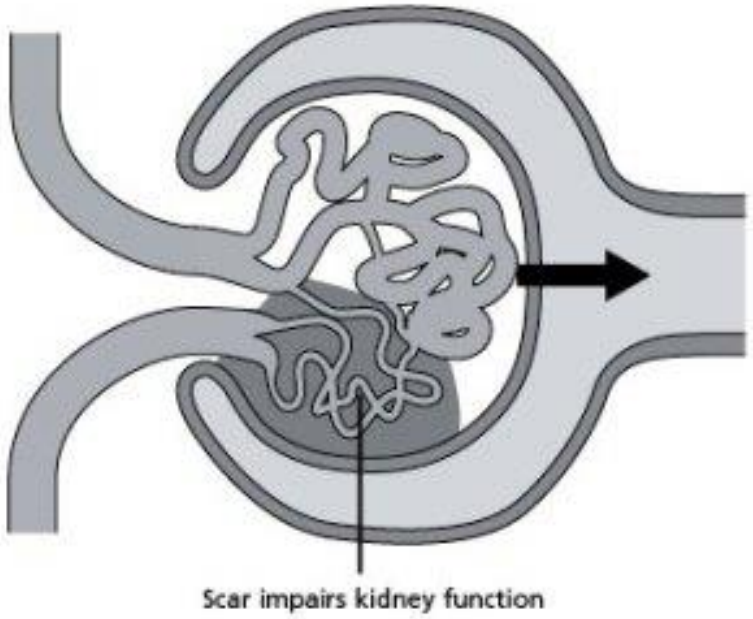
122 MCD pts, 80-90% responded, most CR, some PR, Relapse 26%

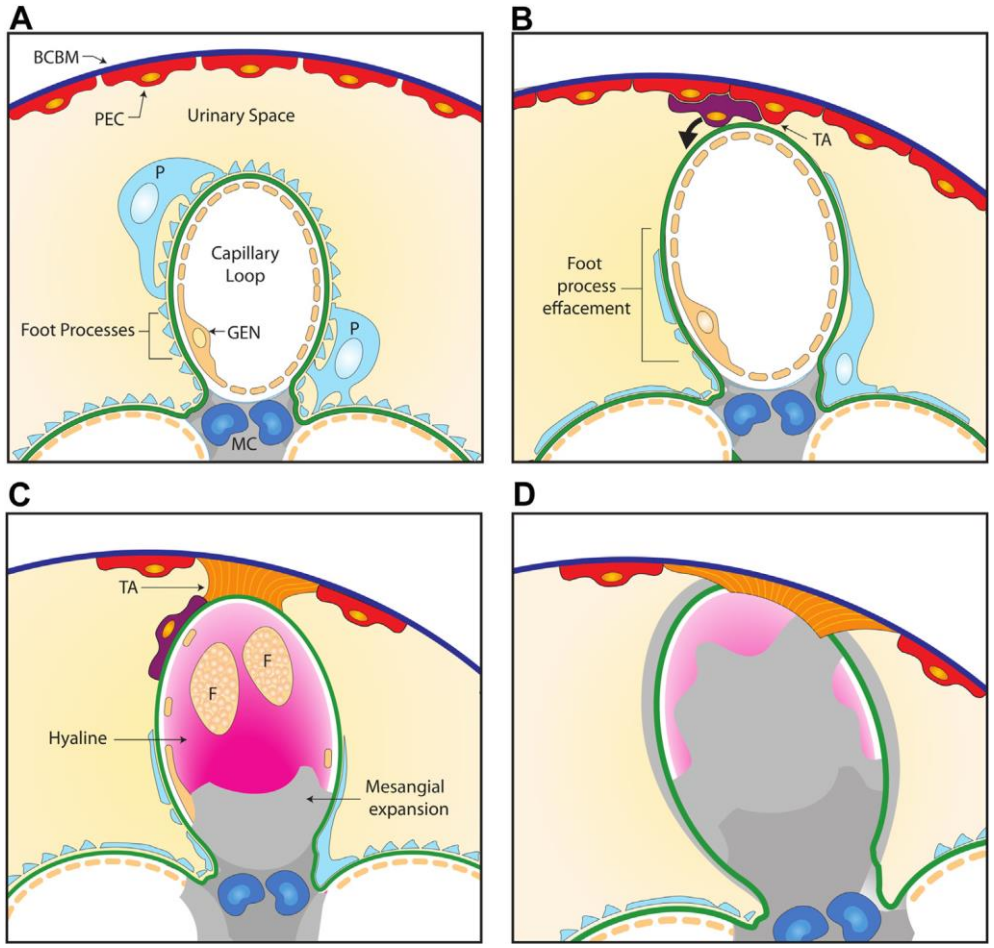
First author	Disease	Previous therapies	Proteinuria (at the time of RTX)	Proteinuria (at the time of last follow-up)	Follow-up time, months	Relapses after RTX	Steroids prior RTX	Steroids at 12 months follow-up
Fernandez-Fresnedo [7]	FSGS (8)	Tac (3), MMF (7), CSA (7), CPA (2)	NRP (8)	PR (2), NR (6)	12–24	–	0.3–1 mg/kg body weight	not reported
Sugiura [8]	MCD (10), FSGS (4)	MMF (2), CSA (8), MZ (2)	CR (4), PR (2), NRP (8)	CR (11), NR (3)	6	1 relapse (1)	21 mg/day (MCD), 23.8 mg/day (FSGS)	11.5 mg/day (MCD), 10 mg/day (FSGS)
Kong [9]	MCD (7), FSGS (4)	MMF (4), AZA (1), CSA (4), CPA (5), plasma exchange (1), IL-5 receptor antagonist (1)	not reported[a]	CR (7), PR (3), NR (1)	11.8–49.3	1 relapse (2), 2 relapses (1)	not reported	at least 50% reduction after 3 months
Munyentwali [10]	MCD (17)	Tac (2), MMF (12), CSA (13), CPA (4), levamisole (7), mechlorethamine (3), chlorambucil (1), perfloxacin (1), basiliximab (1)	CR (6), PR (8), NRP (3)	CR (15), NR (2)	5.1–82.2	1 relapse (4), 2 relapses (1), 3 relapses (1)	40 mg/day	5.2 mg/day
Takei [11]	MCD (25)	MMF (3), CSA (20), MZ (5)	CR (9), PR (8), NRP (6)	CR (24), NR (1)	12	1 relapse (4)	26.4 mg/day	1.1 mg/day
Bruchfeld [12]	MCD (16)	Tac (1), MMF (4), AZA (2), CSA (3), CPA (5), levamisole (2), LDL-apheresis (1), leukeran (1)	CR (2), PR (5), NPR (9)	CR (13), PR (2), NR (1)	12–70	1 relapse (6), 2 relapses (1)	25.6 mg/day	2.3 mg/day
Ruggenenti [3]	MCD (15), FSGS (5),	MMF (9), AZA (1), CSA (9), CPA (7)	CR or PR (20)	CR or PR (20)	12	at least 1 relapse (8)	0.27 mg/kg body weight[b]	0 mg/kg body weight[b]
El-Reshaid[c] [13]	MCD (32), FSGS (18)	all patients received CPA and a large proportion CSA	CR (24), PR (16), NRP (10)	CR (29), PR (19), NR (2)	12	1 relapse (2)	not reported	not reported

Summary

- current evidence >>> support the use of RTX in SD/FR MCD
- >>> need for a properly designed head-to-head comparison of the efficacy of RTX vs other currently used agents, >>> to establish the superiority & saftey of RTX (vs CPA, CsA, MMF)
- trial should have an extended F/U & safety comparing RTX to other currently used agents

FSGS


Scar impairs kidney function


A
BCBM
PEC
Urinary Space
P
Capillary Loop
Foot Processes
GEN
P
MC
B
TA
Foot process effacement
C
TA
F
F
Hyaline
Mesangial expansion
D

FSGS

- FSGS is estimated to be responsible for **40%** of adult nephrotic syndromes and 20% of pediatric nephrotic syndromes and has an incidence of 7 per million.

- FSGS has an estimated prevalence of 4% and is **the most common *primary* glomerular disease** resulting in **ESRD** in the United States

What is FSGS ?!

- FSGS: is not a single diseases – not yet appropriate to call it a disease!
- FSGS: is a “**diagnostic term**” for a “**clinical-pathologic syndrome**” that has “**multiple causes** & **multiple pathogenic mechanism**”
- FSGS: it may be **pathogenically, heterogeneous** !

Moment of Treatment	Children	Adults
Initial treatment nephrotic syndrome	Prednisone (2 mg/kg/d, max 60 mg) for 4-6 wk, followed by 1.5 mg/kg (max 40 mg) on alternate days with tapering over a period of 2-5 mo.	Prednisone (1 mg/kg/d, max 80 mg) for a maximum period of 16 wk. • Remission: slowly tapering over a period of 6 mo. • No remission: tapering over a period of 6 wk.
Infrequent relapses nephrotic syndrome	Prednisone (2 mg/kg/d, max 60 mg) until the child has been in remission for at least 3 d. Thereafter, 1.5 mg/kg (max 40 mg) on alternate days at least 4 wk.	Prednisone (1 mg/kg/d, max 80 mg) until remission and slowly tapering over a period of 6 mo.
Frequently relapse or SDNS	(1) Cyclophosphamide 2 mg/kg/d for 8-12 wk (after steroid-induced remission). (2) Chlorambucil 0.1-0.2 mg/kg/d for 8 wk (alternative for cyclophosphamide). (3) Levamisole 2.5 mg/kg on alternate days for >12 mo (4) CNI (CsA 4-5 mg/kg/d or tacrolimus 0.1 mg/kg/d) for at least 12 mo. Monitor CNI levels during therapy to limit toxicity. (5) MMF 1200 mg/m^2/d for at least 12 mo. (6) Rituximab (off-label) should be considered only in children with FRNS or SDNS who have continuing frequent relapses despite optimal combinations of prednisone and steroid-sparing agent and/or who have serious adverse effects of therapy.	(1) Cyclophosphamide 2-2.5 mg/kg/d for 8 wk. (2) CNI (CsA 3-5 mg/kg/d or tacrolimus 0.05-0.1 mg/kg/d) for 1-2 y. Monitor CNI levels during therapy to limit toxicity. (3) MMF 500-1000 mg twice daily in case of intolerance for steroids, cyclophosphamide, or CNI.
SRNS	(1) CNI for 6 mo (extend to 12 mo if partial remission achieved). (2) If no remission after CNI, MMF (with or without high-dose prednisone).	(1) CsA (3-5 mg/kg/d) for at least 4-6 mo (prolonged if partial or complete remission of 12 mo, followed by slow taper). (2) If CsA not tolerated: MMF 500-1000 mg twice daily with high-dose dexamethasone.

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BRIEF REPORT

Kerstin Benz · Jörg Dötsch · Wolfgang Rascher · Daniel Stachel

Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy

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Abstract A 16-year-old patient with steroid-dependent nephrotic syndrome with more than 35 relapses developed severe relapsing idiopathic thrombocytopenic purpura (ITP). At the age of 2 years, nephrotic syndrome was diagnosed and successfully treated with a standard prednisone regimen. Frequent relapses occurred. Treatment with oral cyclophosphamide followed by cyclosporine was successful, but several attempts to withdraw steroids failed and the patient suffered from multiple relapses. At the age of 12 years, renal biopsy revealed focal segmental glomerulosclerosis and cyclosporine toxicity. A second course of oral cyclophosphamide was unsuccessful and tacrolimus resulted in the development of diabetes mellitus, which was reversed after discontinuation of the drug. At the age of 15 years the patient, still being steroid dependent, developed ITP. Neither steroids nor intravenous immunoglobulins induced permanent remission. Only weekly immunoglobulin infusions could temporarily restore the platelet count. To treat ITP in this desperate situation we decided to deplete B-cells with the monoclonal anti-CD20 antibody rituximab. Intravenous infusions of rituximab (375 mg/m^2) were given once weekly for 4 consecutive weeks without adverse events. Four weeks after the first rituximab dosage, the thrombocyte count increased to normal values. There has been no subsequent relapse of either thrombocytopenia or nephrotic syndrome (on cyclosporine, without steroids) to date. We conclude that B-cell depletion with rituximab might have altered the course of steroid-dependent nephrotic syndrome in our patient.

Introduction

Most pediatric patients with primary nephrotic syndrome respond well to steroid therapy. Patients with frequent relapses or steroid dependency often experience serious side effects of steroids. Alkylating agents such as cyclophosphamide are the drugs of choice [1] in patients with steroid dependence. Cyclosporin A is used if steroids and cyclophosphamide have to be stopped [2]. Nevertheless, some patients remain steroid dependent despite this therapy. For these patients various therapeutic strategies have been suggested, including other immunosuppressive agents such as tacrolimus [3] or mycophenolate mofetil [4, 5], or the immunostimulatory drug levamisole [6]. However, these strategies often fail to maintain complete remission of nephrotic syndrome [7].

Recently, the efficacy of rituximab was investigated in patients with idiopathic membranous nephropathy [8, 9]. Rituximab binds to CD20 with high affinity, killing CD20+ cells in vitro by both complement-mediated lysis and antibody dependent cell-mediated cytotoxicity. In vivo rituximab is effective in the depletion of peripheral blood and lymph node B-cells [10, 11]. It is successfully used in patients with B cell lymphoma [12], post-transplant lymphoproliferative disorders [13], and idiopathic thrombocytopenic purpura (ITP) [14].

Case report

RTX in FSGS

Table 3 Characteristics of discussed studies of rituximab in FSGS

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Fernandez-Fresnedo et al[26]	Retrospective case series	Eight patients with FSGS resistant to steroids and other treatments, all patients had nephrotic range proteinuria at baseline with a mean of 14±4.4 g/24 h	Variable: five patients received 4 weekly doses at 375 mg/m^2 One patient received 4 weekly doses at 375 mg/m^2 initially and again at month 12 One patient received 4 weekly doses at 375 mg/m^2 initially and 2 weekly infusions at month 6 One patient received 8 weekly doses at 375 mg/m^2	24-hour proteinuria Serum creatinine Adverse events	Two patients had significant decrease in proteinuria to 3.2 and 3.9 g/day One patient had transient decrease in proteinuria Five patients failed to respond to rituximab therapy with no significant decrease in proteinuria Serum creatinine increased from 1.4±0.5 to 2.2±1.8 mg/dL No adverse events during follow-up
Ochi et al[27]	Case series	Two patients with steroid-resistant FSGS, and two patients with steroid-dependent FSGS	Single dose at 375 mg/m^2	Complete remission (not defined in the manuscript)	CR achieved in the two patients with steroid-dependent FSGS The two patients with steroid-resistant FSGS did not respond to therapy
Ruggenenti et al[28]	Prospective, open-label, longitudinal, within-patient controlled study	30 patients (ten children, 20 adults) with steroid-dependent or frequently relapsing nephrotic syndrome (included eight patients with FSGS, five adults, three children)	Single dose at 375 mg/m^2 (28 patients) Or two doses of rituximab (two patients)	Number of relapse of nephrotic syndrome in the year after rituximab therapy vs the year before rituximab therapy Side effects	Fivefold decrease in number of relapse in all patients and in patients with FSGS No treatment-related adverse events

Summary

- available evidences >>> do not support the role of RTX in the management of FSGS
- not encouraging !
- >>> different underlying mechanism in FSGS !!! whereby B cells are not the MAIN ROLE players !
- RCT >>> role of RTX (if any) >>> SD/FR FSGS

Study	Patients (n)	Age (y); Duration Disease (y)*	375 mg/m² Once Weekly	FU (mo)	Remission (%)	Relapse (%)	Time to Relapse (mo)*	Remarks
Retrospective studies								
Prytula 2010[31]	28	NA; NA	1-4 doses 2° course: n = 5	1-10	36	46	6 (1-16)	• No data available about indication and timepoint of repeated course rituximab. • 5 patients without response to rituximab.
Ito 2011[32]	7	13.8 ± 5.2; 6.3 ± 3.3	1 dose 2° course: n = 3	12	14	86	NA	• 2° course because of relapse (timepoint not available). • Steroid-induced remission before rituximab administration.
Gulati 2010[33]	24	11.7 ± 2.9; 8.9 ± 2.9	2° course: n = 1	12	83	17	11.2 (8-14)	• At end FU at 12-38 mo: sustained remission in 17 patients. • Steroid-induced remission before rituximab administration.
Kemper 2012[34]	37	13.4 (6.4-18.2); 2.0-14.8	1-4 doses ≥2 course: n = 19	12 24	70 32	30 68	– –	• No data available about indication of repeated courses rituximab. • Overall time to relapse after initial course rituximab: 9.6 mo (5.2-64.1).
Ito 2013[35]	55	4.5 (0.9-16.3); 4.8 (0.2-14.7)	1.8 ± 1.4 doses (range 1-7)	7-31	49	51	5 (1-24)	• Including ≥15 patients from other studies.[32,40,41] • Steroid-induced remission before rituximab administration.
Tellier 2013[36]	18	13.5 (5.9-18); 10.4 (3.5-16)	1-4 doses ≥2 courses: n = 15	24	44	56	13 (5-22)	• Repeated courses when relapse or CD19 >1% • Steroid-induced remission before rituximab administration.
Kronbichler 2013[37]	5	29.2 ± 3.9; 18.3 ± 10.2	1-4 doses	14	100	0	NA	• Childhood onset: 3; adult onset: 2. • After total FU (range 14-55 mo) 1 relapse after 23 mo. • Steroid-induced remission before rituximab administration in 2 patients, 3 patients with proteinuria.

2013[38]		(1.8-30.5)					(range 4.8-16.3)	onset: 5. • Steroid-induced remis before rituximab administration in 10 pa 7 patients with protein
Prospective studies								
Ravani 2013[43]	46	9.9 ± 4.3; 6.3 ± 4.1	1-5 doses	12	20	80	NA	• Including long-term FU of 27 children from previous study.[46] • Inclusion criteria: neve a remission without IS therapy. • Relapse: presence of proteinuria or restart of IS after complete withdrawal of IS thera • Steroid-induced remis before rituximab administration.
Sellier-Leclerc 2012[44]	30	12.9 (3.7-19.7); 9.5 (0.3-17.5)	1-4 doses ≥2 courses: n = 30	26-52	60	40	NA	• Repeated courses to maintain B cell depleti for at least 15 mo. • Steroid-induced remis before rituximab administration.
Kamei 2009[40]	12	12.7 (5-19); 7.2 (1.5-10.6)	1 dose	12	25	75	4 (0.3-12)	• Relapse rate in 6 mo before/after rituximab: 2.83 (SD 1.19) vs 1.08 (SD 1.08) ($P = .016$). • Steroid-induced remis before rituximab administration.
Fujinaga 2010[41]	10	11.1 ± 4.5; 4.6 (2.8-10.8)	1-2 doses	12	70	30	NA	• At end FU at 16.8 ± 5.! sustained remission ir patients; 5 patients ha a relapse and these pa discontinued the CsA a rituximab infusion. • Relapse rate in 12 mo before/after: 4.1 ± 1.7 vs 0.6 ± 0.6 ($P < .01$). • Steroid-induced remis before rituximab administration.

(Co

Study	Patients (n)	Age (y); Duration Disease (y)*	Rituximab 375 mg/m^2 Once Weekly	FU (mo)	Outcome			Remarks
					Remission (%)	Relapse (%)	Time to Relapse (mo)*	
Guigonis 2008[56]	22	14.3 (6.3-22.1) 11.0 (3.6-16.5)	2-4 doses ≥2 courses (n = 12)	6-39	73	14	7-17	• Including 2 steroid-resistant, CsA-sensitive patients. • Steroid-induced remission before rituximab administration in 15 patients, 7 patients with proteinuria. • Indication repeated courses: when response on first course (defined as no relapse of proteinuria before reappearance of CD19 cells despite IS tapering below the usual threshold of relapse). • 3 patients without response to rituximab.
Hoxha 2011[61]	6	24.8 ± 6.3; 7.9 ± 4.9	1 dose >2 course: n = 5	12	50	50	4-12	• Additional courses rituximab when B cells increased or when proteinuria increased. • At end of FU (17.2 ± 4.8 mo), 5 patients attained complete remission and 1 patient a partial remission after repeated infusions of rituximab. • Proteinuria 0.2-9.4 g/d at moment of rituximab administration.
Takei 2013[45]	25	30 ± 12; 10 ± 8	1 dose 2° course at 6 mo	6 12	88 96	12 4	5-6 12	• In total, 4 different patients with a relapse. • Steroid-induced remission before rituximab administration in 9 patients; 16 patients with proteinuria.
Comparative studies								
Sinha 2012[39]	23	Group 1 (n = 10): 12.2 ± 2.3; 3.6 ± 1.5 (age at onset) Group 2 (n = 13): 12.3 ± 3.0; 3.6 ± 2.2 (age at onset)	2-3 doses in Group 1	12	50 (Group 1) 46 (Group 2)	50 (Group 1) 54 (Group 2)	8.5 ± 5.1 (Group 1) 9.8 ± 5.6 (Group 2)	• Retrospective study. • Group 1 received rituximab treatment; Group 2 received tacrolimus 0.1-0.2 mg/kg/d. • Including 3 patients from another study.[33]

Study	Patients (n)	Age (y); Duration Disease (y)*	Rituximab 375 mg/m^2 Once Weekly	FU (mo)	Outcome			Remarks
					Remission (%)	No Response (%)	Time to Remission (mo)*	
Retrospective studies								
Gulati 2010[33]	33	12.7 ± 9.1; 6.4 ± 4.7	1-4	6	48: CR :27 PR: 21	52	32 d (8-60 d)	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Primary resistance: 24; secondary resistance: 9. • No significant difference in response between primary or late resistance.
Prytula 2010[31]	27	NA	1-5	NA	44:CR:22PR:22	56	NA	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Primary resistance: 13; secondary resistance: 13. • FU after initial response (6-12 mo) : sustained remission: 2/12; relapse: 9/12 (time to relapse: 5 mo (1-16)) (data only available of 11 patients).
Ito 2013[35]	19	NA	2.3 ± 1.4	12	63: CR:31.5 PR:31.5	37	NA	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Including 1 patient with a mutation in *WT1* (no response to rituximab).
Kari 2011[47]	4	9.7 ± 1.5; 2.3 (0.5-5)	1	3	25 (CR)	75	NA	• Definition SRNS: lack of remission despite therapy with prednisone for 4 wk. • Primary resistance: 2; secondary resistance: 2. • FU after initial response: relapse: 1/1 (time to relapse: 4 mo).
Fernandez 2009[50]	8	31 ± 14; 50 ± 35 (mo)	4 doses 2° course (n = 3): • at 6 mo: 2 doses (n = 1) • at 12 mo: 4 doses (n = 2)	1-12	0	100	–	• Definition SRNS: nephrotic syndrome despite prednisone therapy (1 mg/kg per day) for ≥4 mo. At 1 mo: • Proteinuria >50% diminished: 3. At 6 mo: • Sustained >50% decrease of proteinuria: 1 • Relapse: 2. At 12 mo • Proteinuria >50% diminished: 2 (these patients

- ttt with RTX >>> facilitates tapering or withdrawal of other IS mediactions (although for a limited time period).

- pts with SDNS >>> the relapse rate decrease with age >>> many pts eventually will develop complete remission >>> efficacy of RTX cannot be judged reliably >>> risk of over-estimation !

- RTX >>> an attractive alternative IS ttt

Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome

Piero Ruggenenti,*† Barbara Ruggiero,* Paolo Cravedi,* Marina Vivarelli,‡ Laura Massella,‡ Maddalena Marasà,† Antonietta Chianca,* Nadia Rubis,* Bogdan Ene-Iordache,* Michael Rudnicki,§ Rosa Maria Pollastro,‖ Giovambattista Capasso,‖ Antonio Pisani,¶ Marco Pennesi,** Francesco Emma,‡ and Giuseppe Remuzzi,*† for the Rituximab in Nephrotic Syndrome of Steroid-Dependent or Frequently Relapsing Minimal Change Disease Or Focal Segmental Glomerulosclerosis (NEMO) Study Group

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ABSTRACT

The outcome of steroid-dependent or frequently relapsing nephrotic syndrome of minimal change disease (MCD), mesangial proliferative GN (MesGN), or FSGS may be poor and with major treatment toxicity. This academic, multicenter, off-on trial (ClinicalTrials.gov #NCT00981838) primarily evaluated the effects of rituximab therapy followed by immunosuppression withdrawal on disease recurrence in 10 children and 20 adults with MCD/MesGN (n=22) or FSGS who had suffered ≥2 recurrences over the previous year and were in steroid-induced remission for ≥1 month. Participants received one dose (n=28) or two doses of rituximab (375 mg/m^2 intravenously). At 1 year, all patients were in remission: 18 were treatment-free and 15 never relapsed. Compared with the year before rituximab treatment, total relapses decreased from 88 to 22 and the per-patient median number of relapses decreased from 2.5 (interquartile range [IQR], 2–4) to 0.5 (IQR, 0–1; P<0.001) during 1 year of follow-up. Reduction was significant across subgroups (children, adults, MCD/MesGN, and FSGS; P<0.01). After rituximab, the per-patient steroid maintenance median dose decreased from 0.27 mg/kg (IQR, 0.19–0.60) to 0 mg/kg (IQR, 0–0.23) (P<0.001), and the median cumulative dose to achieve relapse remission decreased from 19.5 mg/kg (IQR, 13.0–29.2) to 0.5 mg/kg (IQR, 0–9.4) (P<0.001). Furthermore, the mean estimated GFR increased from 111.3±25.7 to 121.8±29.2 ml/min per 1.73 m^2 (P=0.01), with the largest increases in children and in FSGS subgroups. The mean height z score slope stabilized in children (P<0.01). Treatment was well tolerated. Rituximab effectively and safely prevented recurrences and reduced the need for immunosuppression in steroid-dependent or frequently relapsing nephrotic syndrome, and halted disease-associated growth deficit in children.

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Idiopathic nephrotic syndrome (NS) in children and young adults is almost invariably the clinical counterpart of a continuum of glomerular diseases ranging from the relatively frequent minimal change disease (MCD) and the less frequent mesangial proliferative GN (MesGN), which are predominantly observed in children, to the relatively uncommon FSGS that is observed more frequently in adult patients.[1] In a small minority of patients

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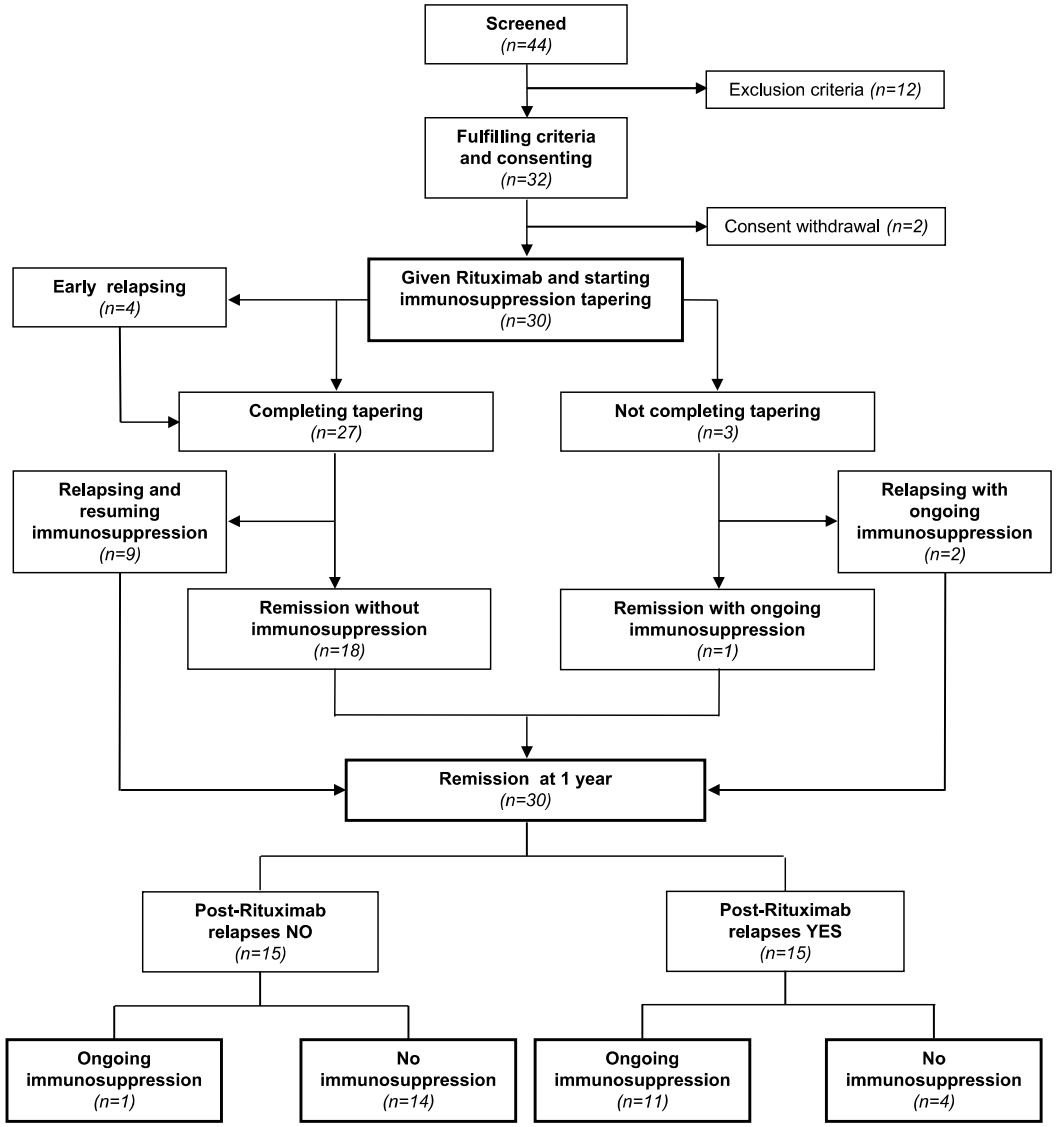

Figure 1. Study flow chart. Of 44 screened patients, 32 fulfill the selection criteria and 30 consent to study participation. Of them, 14 never relapse despite completed withdrawal of steroid and any other immunosuppressant.

Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome

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ABSTRACT

The outcome of steroid-dependent or frequently relapsing nephrotic syndrome of minimal change disease (MCD), mesangial proliferative GN (MesGN), or FSGS may be poor and with major treatment toxicity. This academic, multicenter, off-on trial (ClinicalTrials.gov #NCT00981838) primarily evaluated the effects of rituximab therapy followed by immunosuppression withdrawal on disease recurrence in 10 children and 20 adults with MCD/MesGN (n=22) or FSGS who had suffered ≥2 recurrences over the previous year and were in steroid-induced remission for ≥1 month. Participants received one dose (n=28) or two doses of rituximab (375 mg/m^2 intravenously). At 1 year, all patients were in remission: 18 were treatment-free and 15 never relapsed. Compared with the year before rituximab treatment, total relapses decreased from 88 to 22 and the per-patient median number of relapses decreased from 2.5 (interquartile range [IQR], 2–4) to 0.5 (IQR, 0–1; $P<0.001$) during 1 year of follow-up. Reduction was significant across subgroups (children, adults, MCD/MesGN, and FSGS; $P<0.01$). After rituximab, the per-patient steroid maintenance median dose decreased from 0.27 mg/kg (IQR, 0.19–0.60) to 0 mg/kg (IQR, 0–0.23) ($P<0.001$), and the median cumulative dose to achieve relapse remission decreased from 19.5 mg/kg (IQR, 13.0–29.2) to 0.5 mg/kg (IQR, 0–9.4) ($P<0.001$). Furthermore, the mean estimated GFR increased from 111.3±25.7 to 121.8±29.2 ml/min per 1.73 m^2 (P=0.01), with the largest increases in children and in FSGS subgroups. The mean height z score slope stabilized in children ($P<0.01$). Treatment was well tolerated. Rituximab effectively and safely prevented recurrences and reduced the need for immunosuppression in steroid-dependent or frequently relapsing nephrotic syndrome, and halted disease-associated growth deficit in children.

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All pt in remission at 1 year

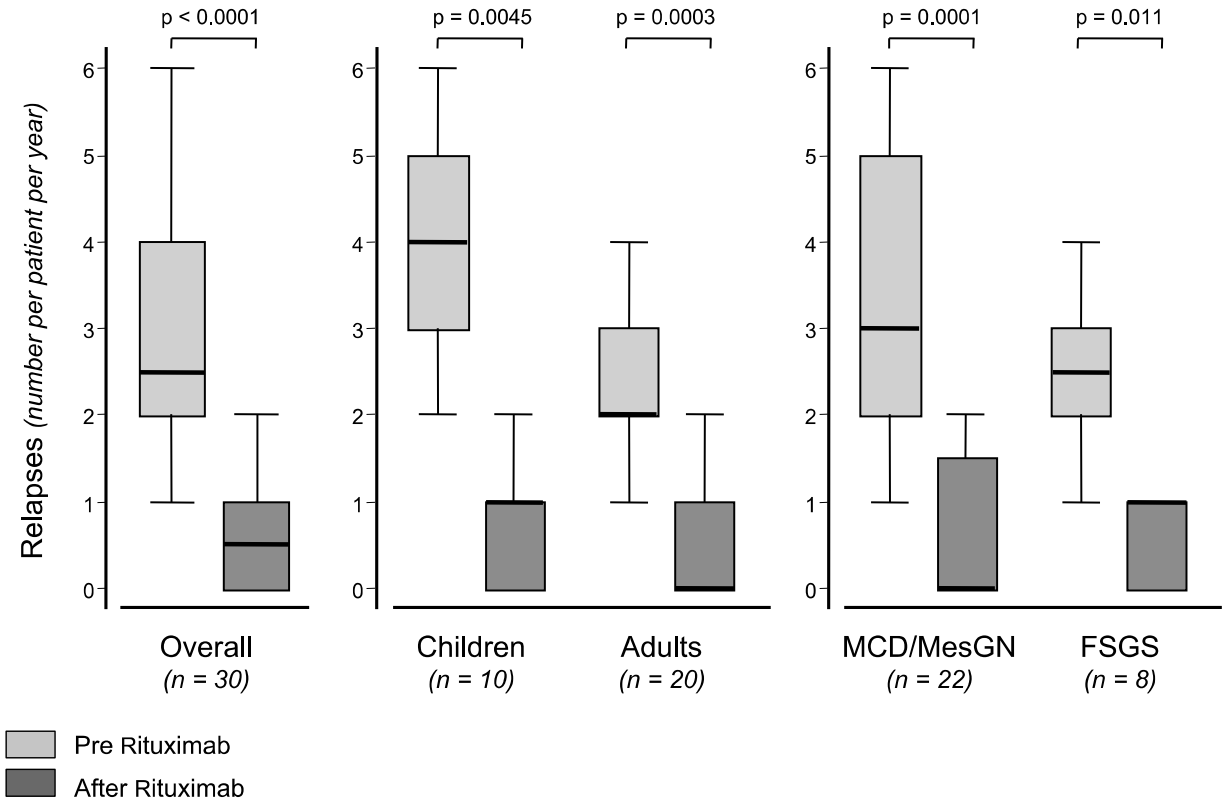

Figure 2. Box plot of the number of NS relapses over 1 year of follow-up after rituximab administration, and during the year before rituximab administration in the study group as a whole (overall), and in different age (children versus adults) and diagnosis (MCD/MesGN versus FSGS) subgroups considered separately.

Reduction for IS

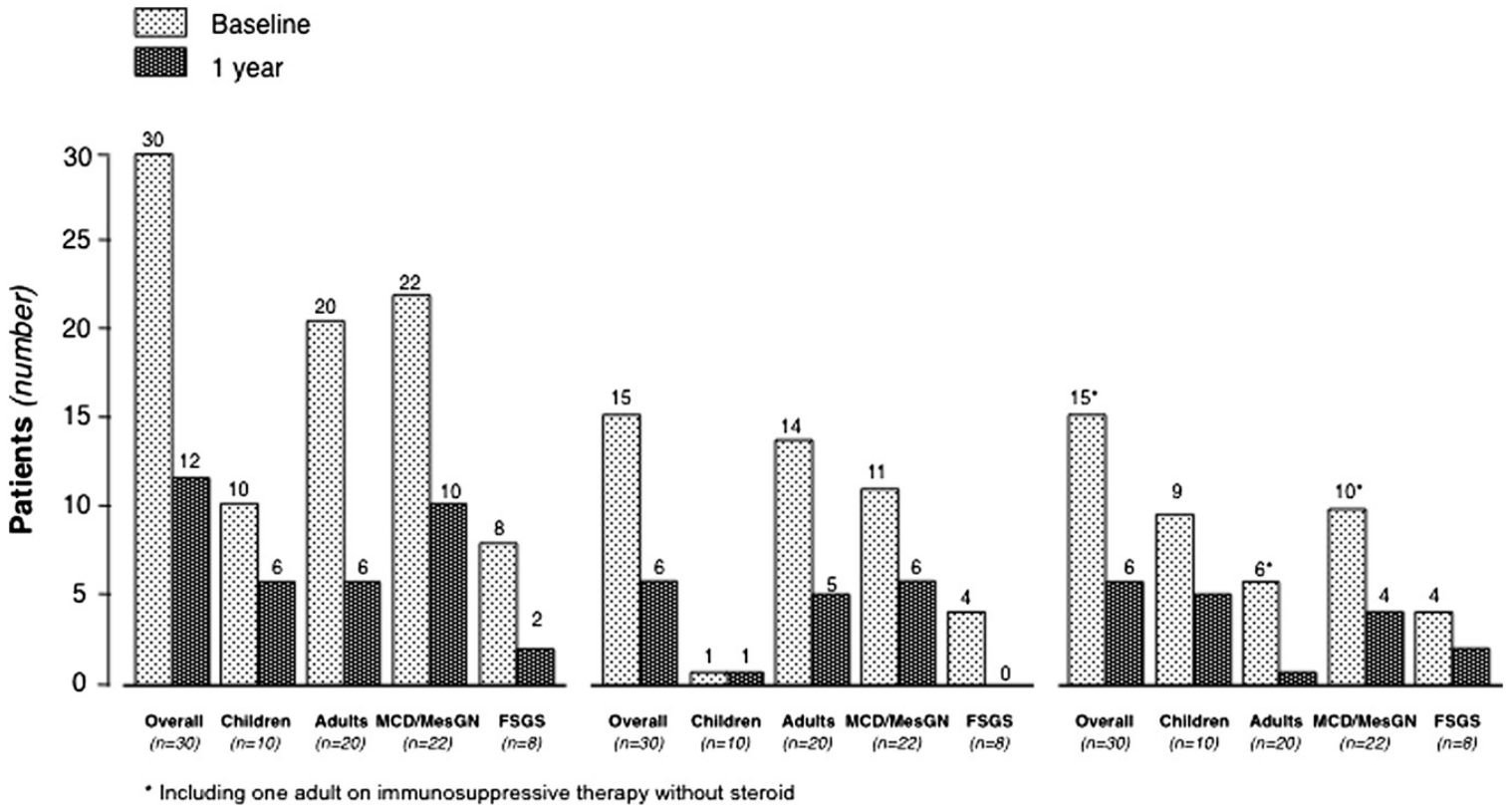

Figure 5. Rituximab reduced the need for maintenance immunosuppression. Numbers of patients with any maintenance immunosuppressive therapy (left), or on maintenance therapy with steroid alone (middle), or steroid plus one or two additional immunosuppressive medications (right) at the time of rituximab administration (baseline) and at 1 year after treatment administration.

Reduction of steroid dose

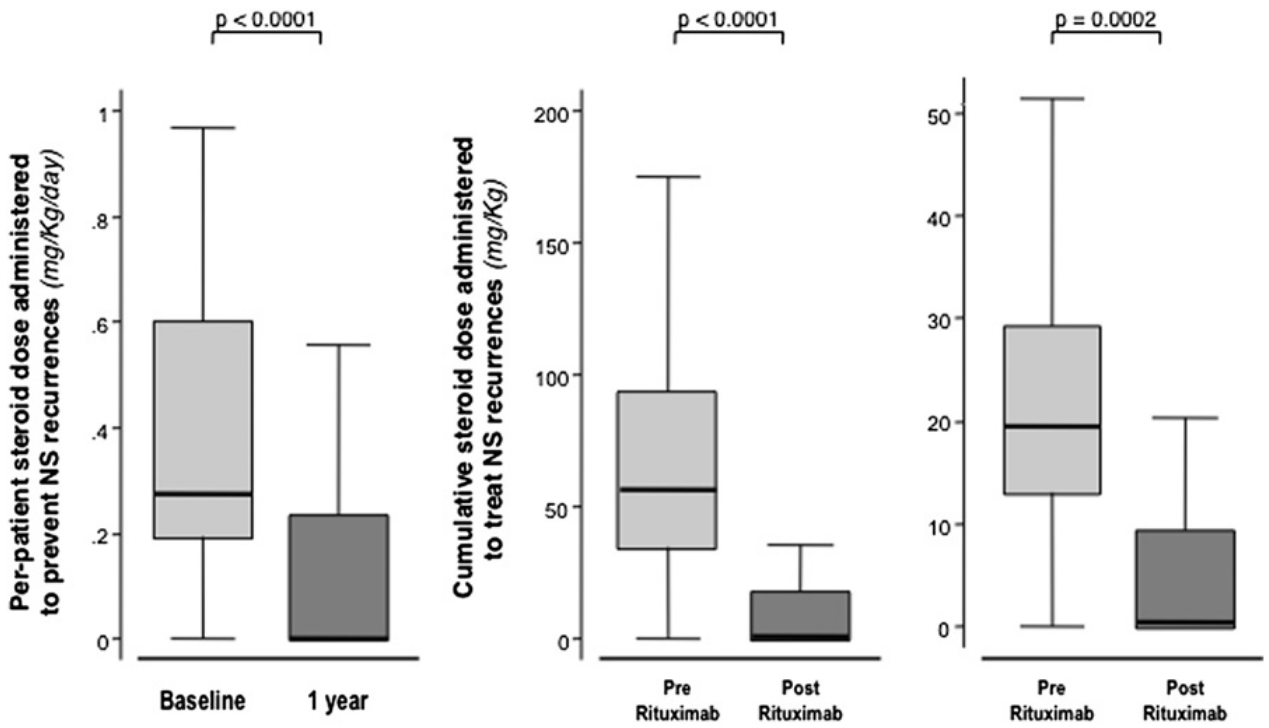

Figure 6. Rituximab allowed to significantly reduce the steroid therapy doses. Box plot of per-patient daily steroid maintenance dose administered to prevent NS recurrences at the time of rituximab administration (baseline) and at 1 year after treatment administration (left), and cumulative steroid dose administered to treat all NS recurrences (middle) and each single NS recurrence (right) observed over 1 year of follow-up after rituximab administration and during the year before rituximab administration. All data are adjusted for patient body weight.

ANOTHER THING...

Bone marrow-derived immature myeloid cells are a main source of circulating suPAR contributing to proteinuric kidney disease

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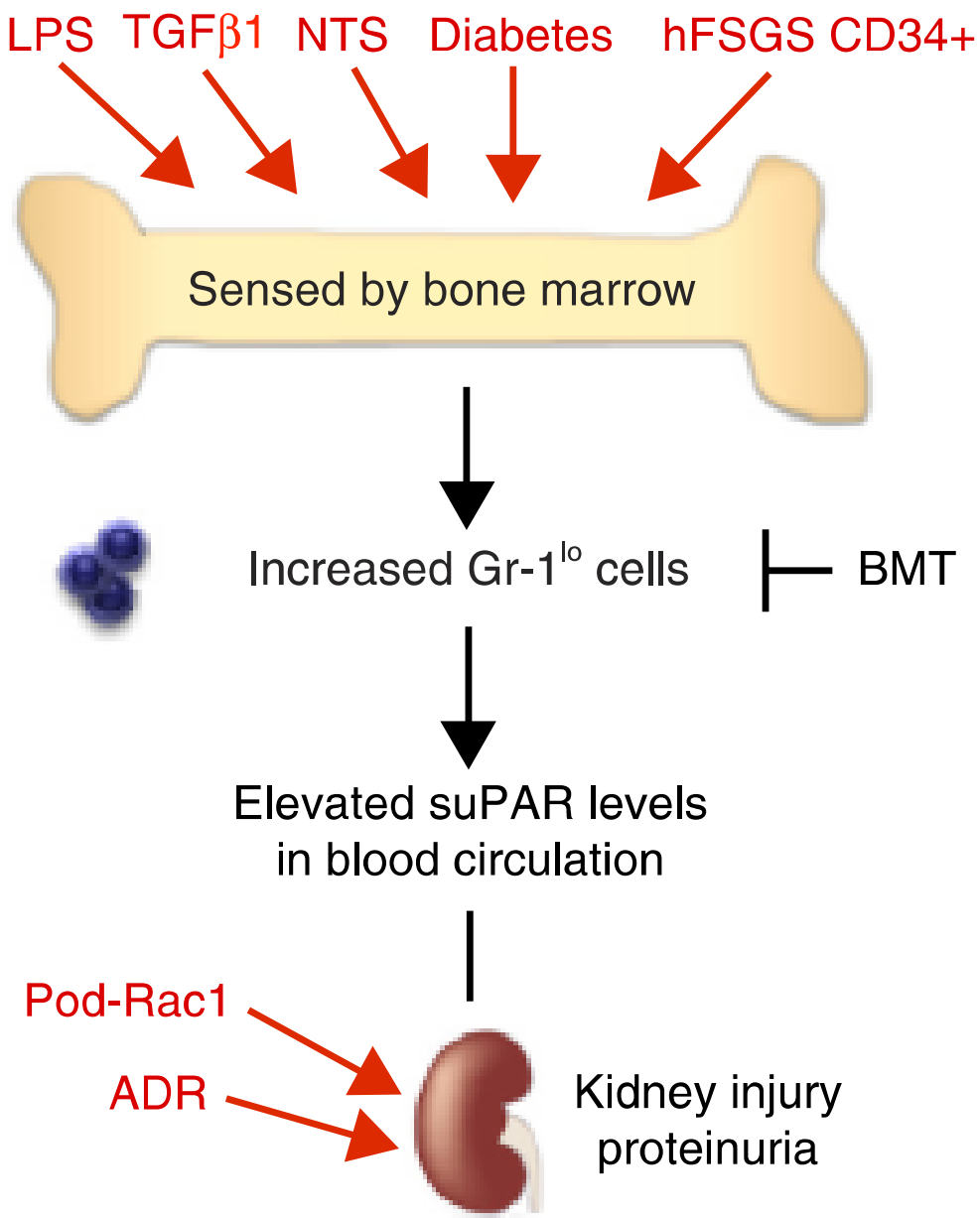
Excess levels of protein in urine (proteinuria) is a hallmark of kidney disease that typically occurs in conjunction with diabetes, hypertension, gene mutations, toxins or infections but may also be of unknown cause (idiopathic)[1]. Systemic soluble urokinase plasminogen activator receptor (suPAR) is a circulating factor implicated in the onset and progression of chronic kidney disease (CKD)[2], such as focal segmental glomerulosclerosis (FSGS)[3,4]. The cellular source(s) of elevated suPAR associated with future and progressing kidney disease is unclear, but is likely extra-renal, as the pathological uPAR is circulating and FSGS can recur even after a damaged kidney is replaced with a healthy donor organ. Here we report that bone marrow (BM) Gr-1^{lo} immature myeloid cells are responsible for the elevated, pathological levels of suPAR, as evidenced by BM chimera and BM ablation and cell transfer studies. A marked increase of Gr-1^{lo} myeloid cells was commonly found in the BM of proteinuric animals having high suPAR, and these cells efficiently transmit proteinuria when transferred to healthy mice. In accordance with the results seen in suPAR-associated proteinuric animal models, in which kidney damage is caused not by local podocyte-selective injury but more likely by systemic insults, a humanized xenograft model of FSGS resulted in an expansion of Gr-1^{lo} cells in the BM, leading to high plasma suPAR and proteinuric kidney disease. Together, these results identify suPAR as a functional connection between the BM and the kidney, and they implicate BM immature myeloid cells as a key contributor to glomerular dysfunction

FSGS is a common primary glomerular disease leading to kidney failure, necessitating dialysis or kidney transplantation[5]. It is characterized morphologically by segmental sclerosis in some glomeruli; clinically, it is characterized by proteinuria[6,7]. About 80% of FSGS cases are primary or idiopathic. FSGS recurs in newly transplanted kidneys in 30% of adults and even more frequently in children[8]. Because of the rapid onset of FSGS recurrence after transplantation, circulating factors have been considered as pathogenic causes[9–12]. We previously reported that suPAR is one such circulating factor in FSGS, and we demonstrated that suPAR binds to and activates β3 integrin on the podocyte membrane. This leads to podocyte foot process effacement and disrupted glomerular barrier function, resulting in proteinuria[3,4]. Furthermore, as relatively high levels of suPAR associate with lower kidney function, prospective cohort studies in humans were subsequently performed: through these, suPAR has recently emerged as a risk factor for the incidence and progression of CKD[2].

Circulating suPAR can be generated by release from the membrane-bound form of urokinase plasminogen activator receptor (uPAR), a glycosylphosphatidylinositol (GPI)-anchored three-domain (DI, DII and DIII) signaling protein[13,14]. suPAR exists in multiple forms due to alternative splicing, protein glycosylation and enzymatic cleavage of the mature protein[15]. While mounting experimental and clinical evidence suggests that suPAR is involved in the pathogenesis of CKD, the cellular source(s) of elevated suPAR remains unknown. Thus, identifying the cellular source(s) of suPAR that are relevant to kidney disease is one essential step required for the exploration of potential therapeutics aimed at the treatment of suPAR-related renal dysfunction such as that seen in FSGS.

Experimental studies have shown that mice injected with lipopolysaccharides (LPS) as a model of glomerular injury display a transient proteinuria associated with podocyte foot process effacement[3,4,16,17], as well as some renal lesions similar to FSGS in humans[18]. Based on our previous findings that uPAR deficiency protects against


LPS
TGFβ1
NTS
Diabetes
hFSGS CD34+
Sensed by bone marrow
Increased Gr-1lo cells
BMT
Elevated suPAR levels
in blood circulation
Pod-Rac1
ADR
Kidney injury
proteinuria

B-CELL DEPLETION AFTER RTX

B Cell Monitoring

- Antibodies that deplete B cells, including rituximab, have demonstrated efficacy
- to identify factors that impact **repopulation of B cells** after depletion therapy >>> analyzed $CD19^+$ B-cell counts
- event of **$CD19^+$ repopulation** ($CD19^+$ cells rising to a level above 1% of total $CD45^+$ lymphocytes after depletion).
- Patients who had higher body surface area (and dosages ranging from 574 mg to 975 mg) had a higher risk of experiencing repopulation than patients with lower body surface area, even when they received an adapted dose

- “It is important **to not miss** the **time point of B-cell repopulation**, as this is most likely **linked to resurging disease activity**, at least in patients with MS and [NMOSD],” write the authors, who note that
- “**monitoring of B cells** is recommended with special attendance to [high–body surface area] patients ***to not miss the early repopulators***.”
- The researchers propose that patients receiving treatment for neurologic diseases be **monitored after 2 and 4 months, then biweekly to every 4 weeks thereafter**.

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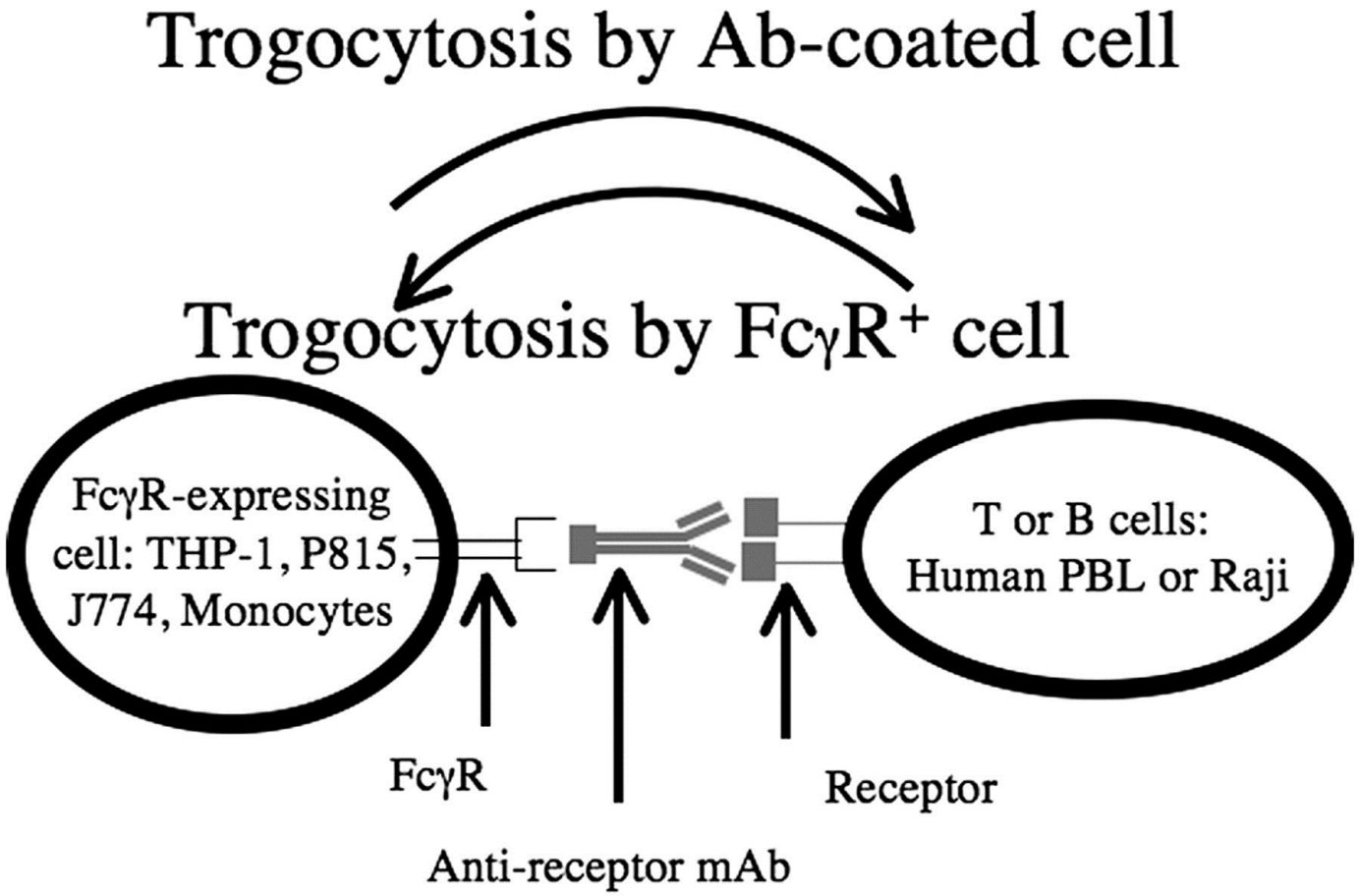
Rituximab Mediates Loss of CD19 on B Cells in the Absence of Cell Death

Jonathan D. Jones, B. JoNell Hamilton, and William F. C. Rigby

CD19 is transferred from B cells to monocytes and neutrophils during shaving of the RTX– CD20 complex in an Fc-dependent manner.

These data suggest that monitoring the effect of RTX by measuring the CD19 cell count may be compromised by this activity.



- future investigations of **B-cell depleting therapies** in neurological diseases should address both **dosing protocol** and **biomarkers** ***beyond CD19^{+}*** cells **in the peripheral blood**;
- potential biomarkers that could prove useful include, **memory and effector B cells.**

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The Journal of Translational Immunology

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Usefulness of monitoring of B cell depletion in rituximab-treated rheumatoid arthritis patients in order to predict clinical relapse: a prospective observational study

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Summary

Our objective was to evaluate the contribution of monitoring B cell subset depletion after rituximab in patients with rheumatoid arthritis (RA) in order to guide reintroduction to forestall relapse. This prospective, monocentre study included all RA patients receiving two 1-g rituximab infusions at a 15-day interval. The patients were followed clinically and biologically every 2 months until rituximab reintroduction. The physician was blinded to lymphocyte-typing results to diagnose relapse and, hence, retreatment. Among the 39 patients included between March 2010 and December 2011 and followed until April 2013, seven received two rituximab cycles, yielding a total of 46 cycles for analysis. After the two rituximab cycles, the total number of $CD19^+$ B cells decreased significantly (0·155 *versus* 0·0002 G/l, $P < 0·0001$), with complete depletions in all patients of $CD19^+CD38^{++}CD24^{++}$ (transitional) ($P < 0·0001$) and $CD19^+CD27^+$ (memory) B lymphocytes. A significant majority of patients relapsed within the 4 months following repopulation of total B ($P = 0·036$), B transitional ($P = 0·007$) and B memory ($P = 0·01$) lymphocytes. $CD19^+$ B lymphocyte repopulation preceded clinical RA relapse and enabled its prediction 4 months in advance. Hence, monitoring of $CD19^+$ B lymphocytes could serve as a tool to predict those relapses.

Keywords: B lymphocyte depletion, rheumatoid arthritis, rituximab

- The results of this study showed that **monitoring B lymphocyte depletion was a reliable tool**, able **to predict clinical** RA **relapse** in **rituximab-treated patients**.
- Indeed, **observing B lymphocyte and subsets regeneration** has a ***high sensitivity to predict clinical relapse***.
- Moreover**, a significant majority** of our cohort ***patients relapsed within 4 months after B cell repopulation***, particularly transitional and memory subsets

Important message

- the contribution of **monitoring B lymphocyte depletion** as a **predictive biological parameter during the follow-up** of rituximab-treated patients **to guide the decision to retreat precociously** to **achieve tight control**

- **B cell depletion “may not be necessary**” for the development of **remission !**

- On the other hand >>> although most relapses occur after B cell recovery, **relapse may occur despite “ongoing B cell depletion” !**
-

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Rituximab in steroid-dependent idiopathic nephrotic syndrome in childhood—follow-up after CD19 recovery

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Abstract

Rituximab (RTX) is a new treatment strategy in high-degree steroid-dependent idiopathic nephrotic syndrome (SDNS) in childhood. Thirty patients (nine girls) with SDNS with steroid side effects and previously treated with immunosuppressive drugs, mostly calcineurin inhibitors, were treated with RTX and included in this non-controlled single-centre study. Patient age at first RTX infusion was 12.9 ± 0.7 years.

Our aim was to evaluate disease outcome after a minimum CD19 depletion period of 15 months obtained by repeated RTX infusion.

Minimum follow-up after initial CD19 depletion was 24 months. During the RTX treatment period, seven patients had nephrotic syndrome relapses, six among them at the time of an intermittent CD19 recovery and one patient relapsed under CD19 depletion. The risk for these patients to relapse after the RTX treatment period was higher than in those without intermittent relapses. After definitive CD19 recovery over a follow-up of 17.4 ± 1.9 months, 19 patients (63%) did not relapse and 11 (37%) relapsed 4.3 ± 1 months after defininitive CD19 recovery. Among these 11 patients, 6 already had intermittent relapses during the RTX treatment period. Steroid and immunosuppressive treatment could be discontinued in all patients during CD19 depletion and was re-introduced in two after CD19 recovery. Fourteen patients had mostly benign and transitory side effects, which did not require RTX discontinuation. In conclusion, RTX treatment with a 15-month CD19 depletion period induced long-term remission after definitive CD 19 recovery in almost two-thirds the of patients without oral immunosuppressive drugs.

Keywords: B cell depletion; idiopathic nephrotic syndrome; immunosuppressive treatment; paediatric; rituximab; side effects

Introduction

Rituximab (RTX) has been proposed as a new treatment strategy to reduce high-degree steroid dependency in childhood idiopathic nephrotic syndrome [1–9]. RTX is used in paediatric idiopathic nephrotic syndrome since 2006, but long-term observational studies are still lacking. Oral immunosuppressive drugs, classically used in this setting, are cyclophosphamide (CP), mycophenolate mofetil (MMF) and calcineurin inhibitors, such as cyclosporine A (CyA) or tacrolimus. Further, steroid dependency is generally replaced by dependency on calcineurin inhibitors and/or MMF, exposing the patient to the risk of relapses in case of non-compliance. Long-term use of calcineurin inhibitors is often limited by nephrotoxicity, while gonadotoxicity has to be considered for patients treated with CP.

Despite the absence of pathophysiological evidence, CD19 depletion was shown to be correlated with remission in the absence of other immunosuppressive drugs [2, 9, 10].

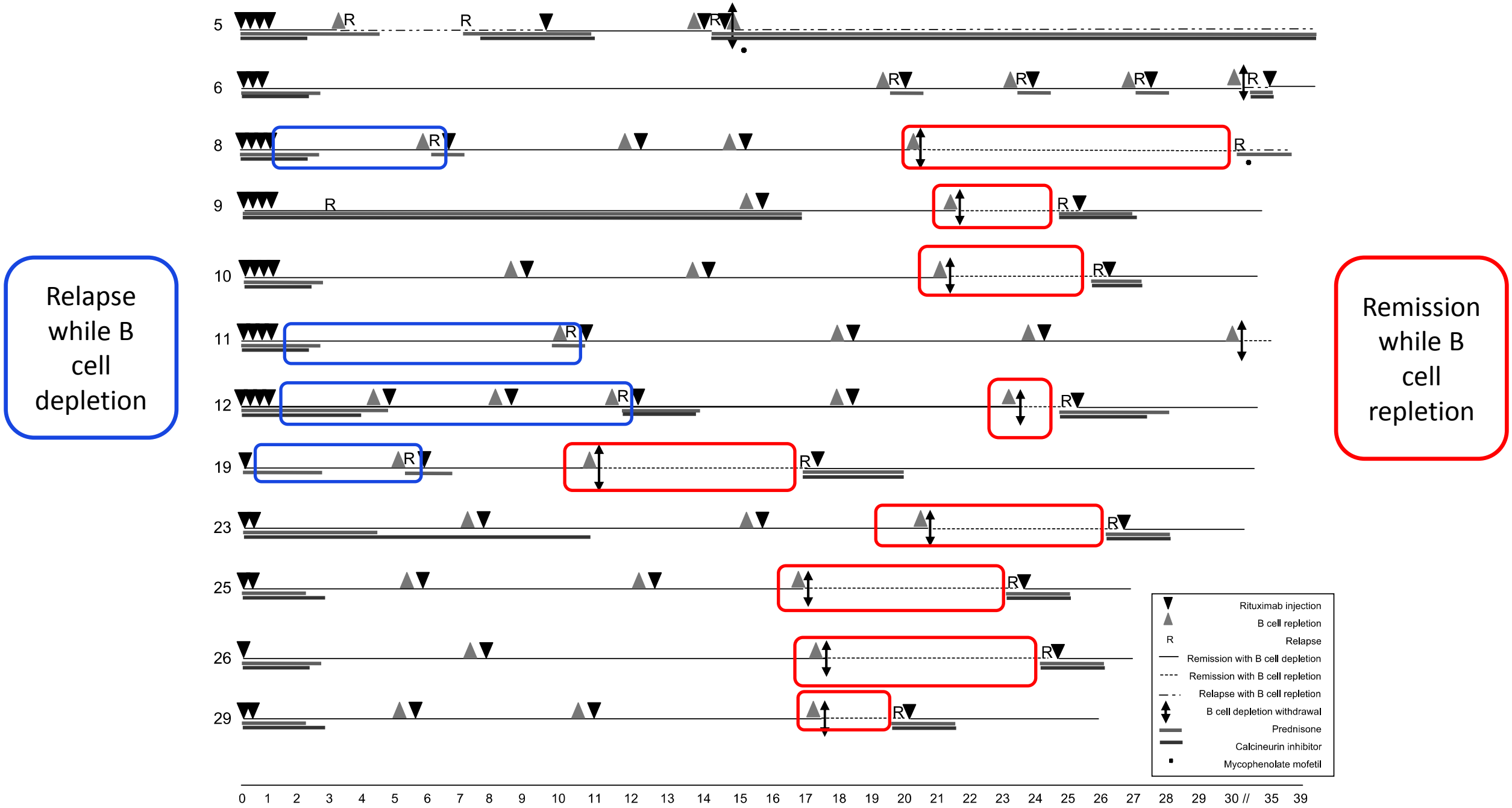

Fig. 4. Clinical course of patients with a relapse after the CD19 depletion period.

- available data on
- >>> ***B cell depletion / B cell recovery in relation to remission & relapse >>> No Clear & established relationship*** !!!
- This *is in line with a study in pts with RA* in which "**no relationship** was found between **B cell depletion & clinical response** and between the **recovery of B cells and the return of disease activity** !

Rituximab Pharmacokinetics in Patients With Rheumatoid Arthritis: B-Cell Levels Do Not Correlate With Clinical Response

Ferdinand Breedveld, Sunil Agarwal, Ming Yin, Song Ren, Nicole F. Li, Tim M. Shaw, and Brian E. Davies

This study characterized the relationship between clinical response, serum rituximab concentrations, and peripheral B-cell levels in patients with rheumatoid arthritis treated with rituximab. Data were analyzed from a double-blind, phase IIa trial in which 161 patients with active rheumatoid arthritis despite continuing methotrexate were randomized to methotrexate alone (10-25 mg/wk), rituximab alone (single course: 1000 mg administered intravenously on days 1 and 15), rituximab plus cyclophosphamide (750 mg administered intravenously on days 3 and 17), or rituximab plus methotrexate. Serum samples for pharmacokinetic analysis were collected through 24 weeks, and peripheral circulating CD19+ B-cell levels were measured through 48 weeks. All treatments were generally well tolerated, with no clinically relevant excess of adverse events leading to withdrawal among patients who received rituximab compared with those who received methotrexate alone. The proportions of patients who achieved an American College of Rheumatology score of 50 at week 24 were 13% (methotrexate alone), 33% (rituximab alone), 41% (rituximab plus cyclophosphamide), and 43% (rituximab plus methotrexate). Peripheral B-cell depletion occurred by day 15 in all patients treated with rituximab. There was no relationship between B-cell depletion and clinical response. Recovery of peripheral B cells was variable and showed no relationship with return of disease activity in patients who responded to rituximab. The mean terminal half-life of rituximab was 19 to 22 days; pharmacokinetic parameters were similar whether rituximab was administered alone or with methotrexate or cyclophosphamide. Because the level of peripherally circulating B cells does not appear to correlate with a maintained clinical response in patients with rheumatoid arthritis, the timing of rituximab retreatment should be based on clinical symptoms rather than peripheral B-cell levels.

Keywords: *Rituximab; pharmacokinetics; pharmacodynamics*

Journal of Clinical Pharmacology, 2007;47:1119-1128

Think Clinical !

Clinical Summary

- B-cell targeted ttt is increasingly used in pts with iNS, such as MCD, and iFSGS
- RTX is equivalent to Std IS in SD-MCD/ SD-iFSGS
- RTX has no role in SR-NS

MERCI