ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

ORKiD FILIÈRE ORPHAN KIDNEY DISEASES

French (PNDS) versus International (KDIGO) recommendations for the management of Idiopathic Nephrotic syndrome in adults

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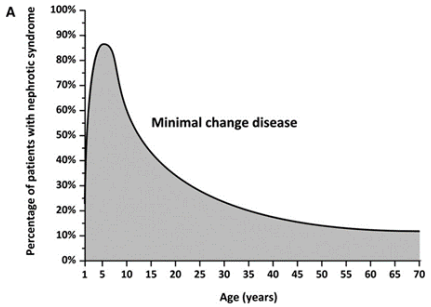
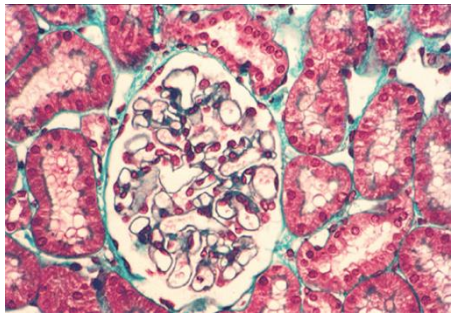
Idiopathic Nephrotic Syndrome

Idiopathic nephrotic syndrome (INS) is a primary glomerular disease, which includes two histological variants MCD and primary (FSGS)

MCD

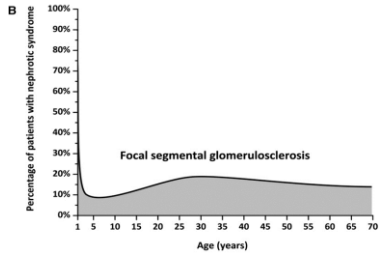
10-15% of nephrotic syndrome in adults
75% o nephrotic syndrome in children

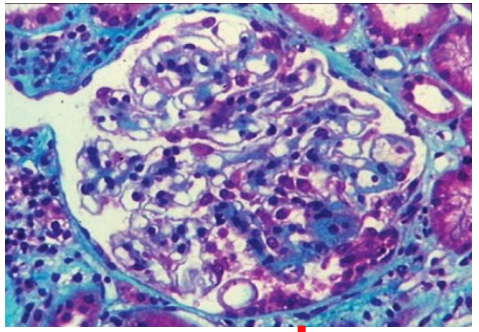




Primary FSGS

30% of nephrotic syndrome in adults
20% of nephrotic syndrome in children

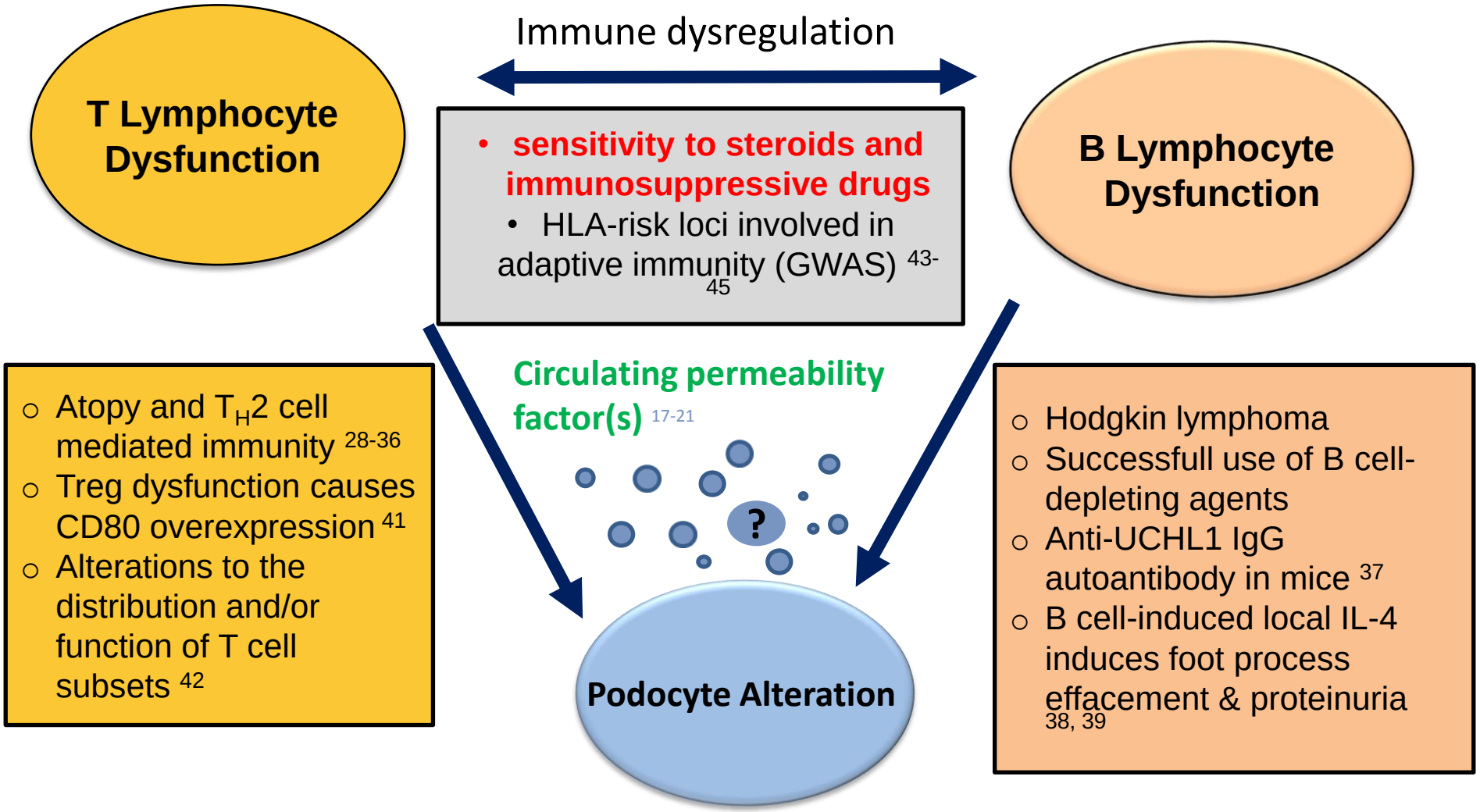




Podocyte Injury

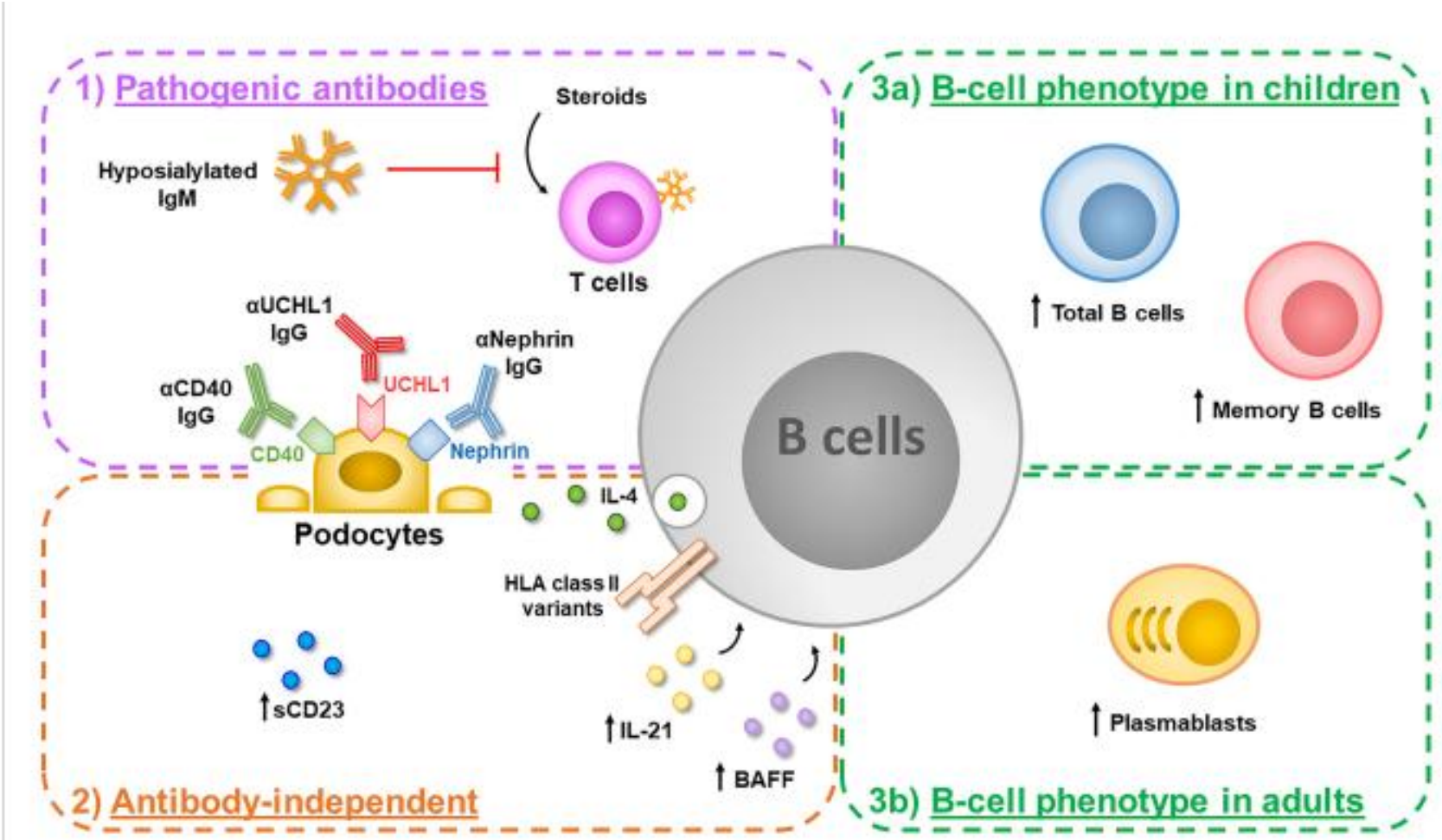
Vivarelli M CJASN 2017
Sahali D Seminars Immunopath2014

Current pathophysiological processes



Gauckler Autoimmunity Reviews 2020

Growing evidence for a key role of B lymphocytes in the pathogenesis of INS



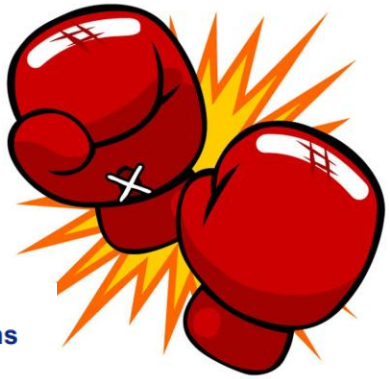
Sensitivity of the disease to anti CD20 monoclonal antibodies

Colucci Frontiers in Immunology 2022

Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases

OPEN

Brad H. Rovin[1], Sharon G. Adler[2], Jonathan Barratt[3], Frank Bridoux[4], Kelly A. Burdge[5], Tak Mao Chan[6], H. Terence Cook[7], Fernando C. Fervenza[8], Keisha L. Gibson[9], Richard J. Glassock[10], David R.W. Jayne[11], Vivekanand Jha[12,13,14], Adrian Liew[15], Zhi-Hong Liu[16], Juan M. Mejía-Vilet[17], Carla M. Nester[18], Jai Radhakrishnan[19], Elizabeth M. Rave[20], Heather N. Reich[21], Pierre Ronco[22,23], Jan-Stephan F. Sanders[24], Sanjeev Sethi[25], Yusuke Suzuki[26], Sydney C.W. Tang[6], Vladimír Tesar[27], Marina Vivarelli[28], Jack F.M. Wetzels[29], Lyubov Lytvyn[30,31], Jonathan C. Craig[32,33], David J. Tunnicliffe[33,34], Martin Howell[33,34], Marcello A. Tonelli[35], Michael Cheung[36], Amy Earley[36] and Jürgen Floege[37]



Protocole National de Diagnostic et de Soins (PNDS)

Syndrome néphrotique idiopathique de l'adulte

Texte du PNDS

Centre de référence du Syndrome Néphrotique Idiopathique de l'enfant et de l'adulte

Avril 2008
Actualisation Novembre 2014

HAS
HAUTE AUTORITÉ DE SANTÉ

Groupe d'experts actualisation du PNDS Syndrome néphrotique idiopathique de l'adulte septembre 2014

Centre de référence syndrome néphrotique idiopathique

Pr AUDARD Vincent, Néphrologue, Créteil Coordonnateur du PNDS

Dr DAHAN Karine, Néphrologue, Paris

Pr DANTAL Jacques, Néphrologue, Nantes

Pr DURRBACH Antoine, Néphrologue Kremlin Bicêtre

Dr HUMMEL Aurélie, Néphrologue Paris

Dr KOFMAN Tomek, Néphrologue Créteil

Pr SAHALI Dil Néphrologue coordonnateur centre de référence SNI

Commission de néphrologie (Société de Néphrologie)

Pr BOFFA Jean-Jacques Néphrologue, Paris (président de la commission de néphrologie de la société de Néphrologie)

Pr CHAUVEAU Dominique, Néphrologue, Toulouse

Dr KARRAS Alexandre, Néphrologue Paris

Dr GUERROT Dominique, Néphrologue, Rouen

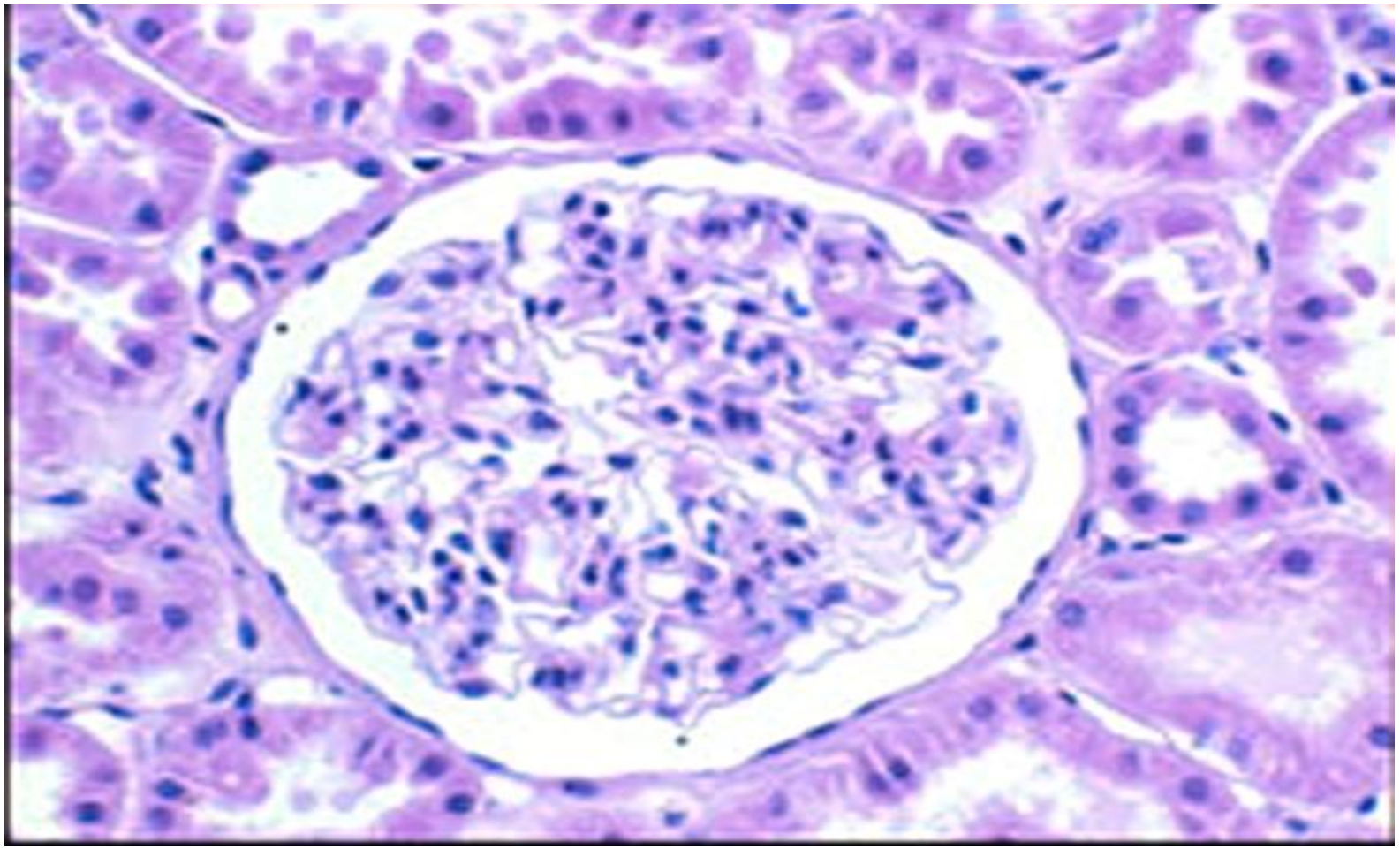
Dr JOURDE- CHICHE Noémie, Néphrologue, Marseille

Pr MOULIN Bruno (président de la société de Néphrologie)

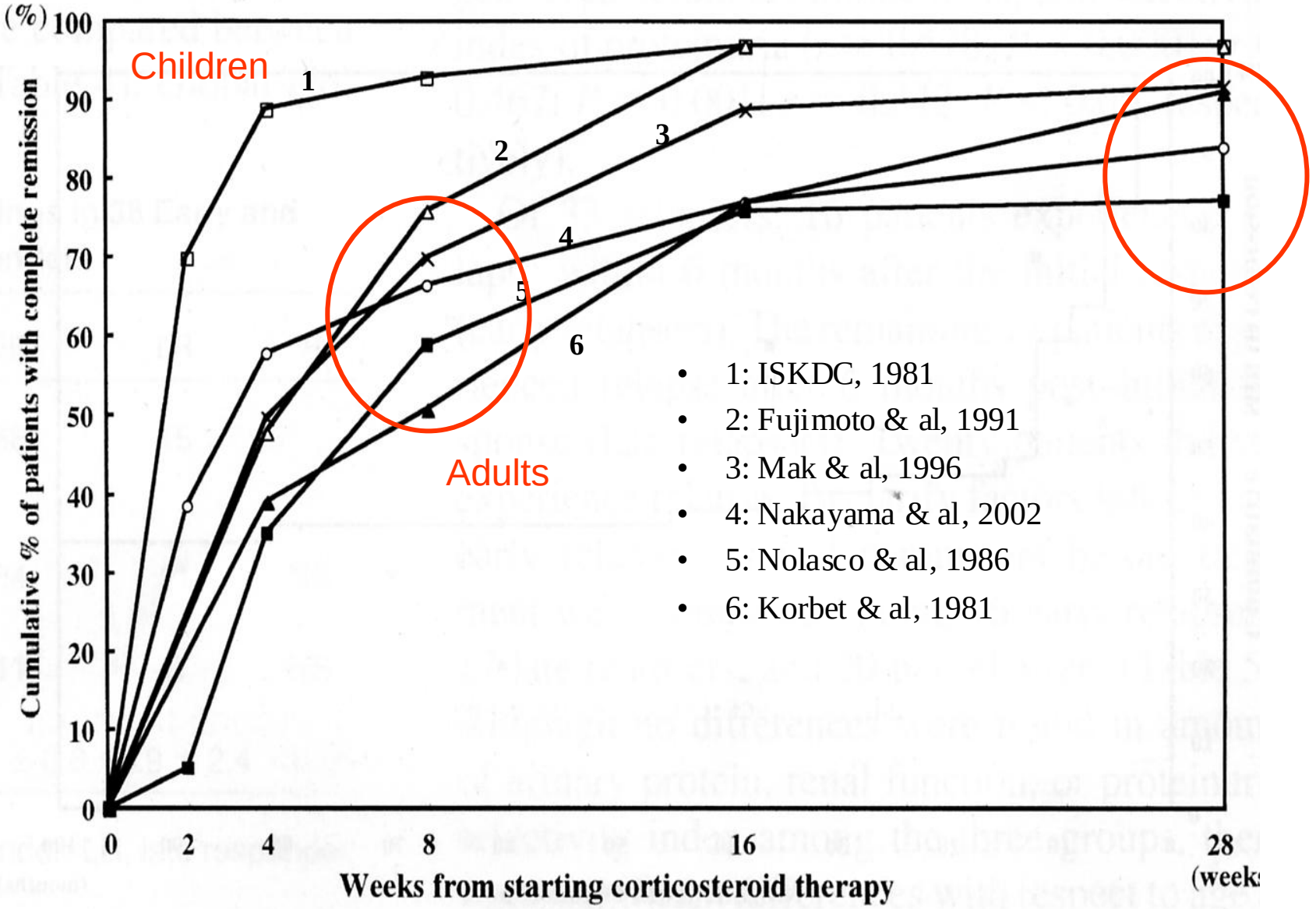
Dr PROVOT François, Néphrologue Lille

Dr VUIBLET Vincent, Néphrologue Reims

Treatment of MCD in adults



Initial treatment for MCD in adults : High-dose oral steroids



Hogan J JASN 2013

http://www.kidney-international.org

The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines—application to the individual patient

Jai Radhakrishnan[1] and Daniel C. Cattran[2]

Chapter 5: MCD in adults

5.1: Treatment of initial episode of adult MCD

5.1.1: We recommend that corticosteroids be given for initial treatment of nephrotic syndrome (1C).

5.1.2: We suggest that prednisone or prednisolone (prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in randomized controlled trials depending on the country of origin; all later references to prednisone in this chapter refer to prednisone or prednisolone; all later references to oral corticosteroids refer to prednisone or prednisolone) be given at a daily single dose of 1 mg/kg (maximum 80 mg) or at an alternate-day single dose of 2 mg/kg (a maximum dose of 120 mg). (2C)

5.1.3: We suggest that the initial high dose of corticosteroids, if tolerated, be maintained for a minimum period of 4 weeks if complete remission is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. (2C)

5.1.4: In patients who remit, we suggest that corticosteroids be tapered slowly over a total period of up to 6 months after achieving remission. (2D)

5.1.5: For patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis), we suggest treatment with oral CYC or CNIs as discussed in FR minimal-change disease (MCD). (2D)

5.1.6: We suggest using the same initial dose and duration of corticosteroids for infrequent relapses as in Recommendations 5.1.2, 5.1.3, and 5.1.4. (2D)

Initial treatment for MCD in adults : High-dose oral steroids

Oral versus IV

81 patients

n = 29 IV pulses 1 gr 3jrs followed by oral steroid regimen from 30 to 40 mg/day during 4 to 8 weeks

Vs

N= 52 1mg/kg/jr 4 à 8 semaines

- **Delay of remission** 15,2 jrs +/- 10 (IV)
  26,7 jrs +/-17 (oral)
  p =0,0266

- **Remission rate** 12 weeks
  86,2% (IV) vs 96,2% (Oral)
  p =NS

Fukudome K Nephrology 2012

Table 1. Clinical characteristics of 65 patients treated with initial methylprednisolone use followed by prednisolone (methylprednisolone+prednisolone group) and 60 patients treated with initial prednisolone use (prednisolone group)

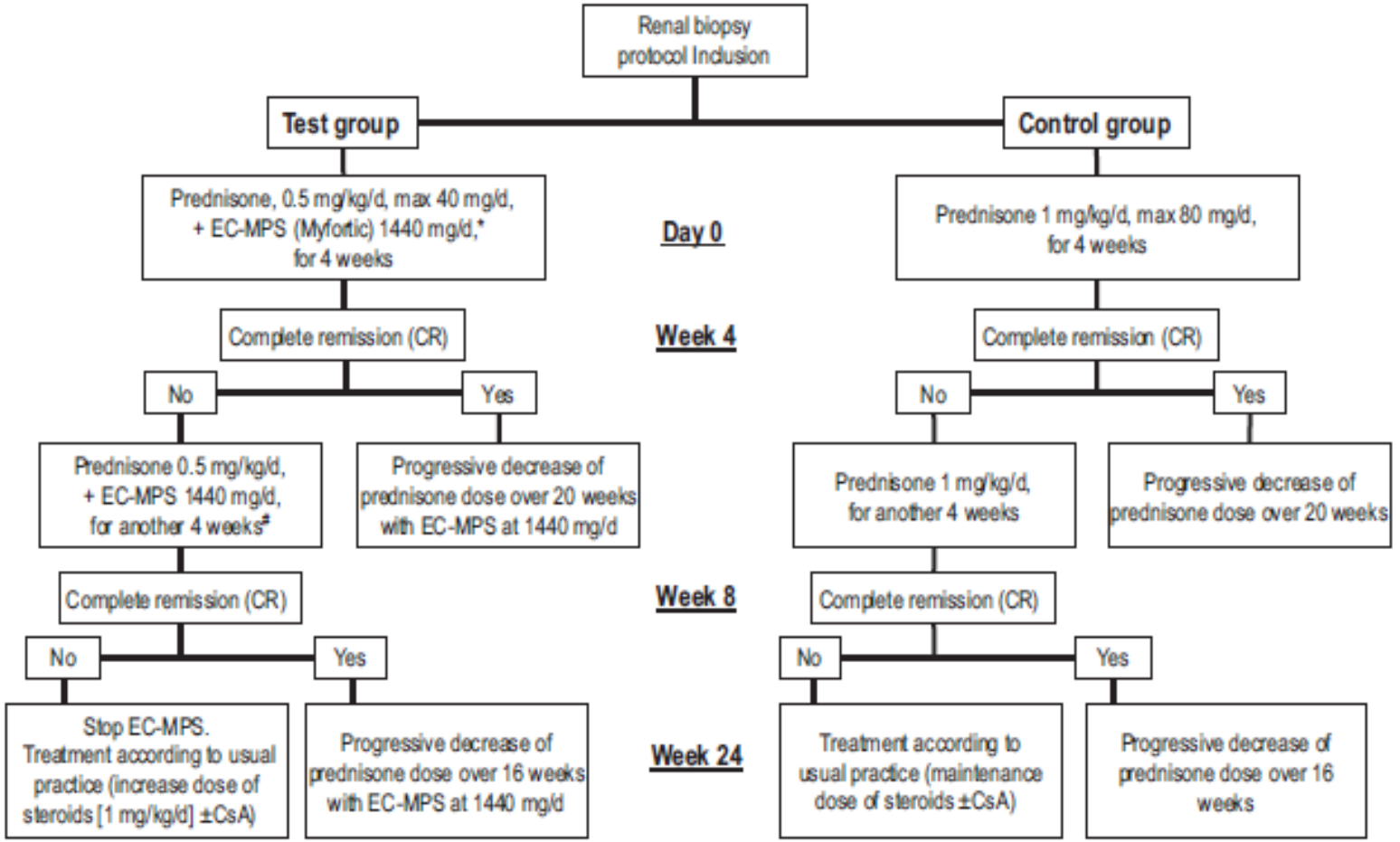
Patient Characteristics	Initial Use of Corticosteroid		*P* Value
	mPSL+PSL[a]	PSL	
Number	65	60	
Remission and relapse during observational period			
First remission, *n* (%)	65 (100.0)	58 (96.7)	
Time to first remission, d[b]	11 [8−20]	19 [12−37]	<0.001
First relapse, *n* (%)[b]	32 (49.2)	43 (74.1)	0.01
Time to first relapse, yr[c]	1.0 [0.6−1.5]	0.8 [0.4−1.6]	0.17
Entire observational period, yr	3.5 [1.8−6.4]	4.0 [2.1−7.9]	0.17
Total number of relapses, *n* per person[d]	0 (0−8)	1 (0−9)	
Incidence of relapse, per person-yr[d]	0.0 [0.0−0.5]	0.5 [0.0−0.7]	0.007

Similar remission rates and no changes in subsequent relapse rates

Shinzawa CJASN 2014

Initial treatment for MCD in adults : Alternative first line therapy

Steroid sparing option : MMF and low dose of steroids (MSN study)



STUDY DESIGN OF MSN trial

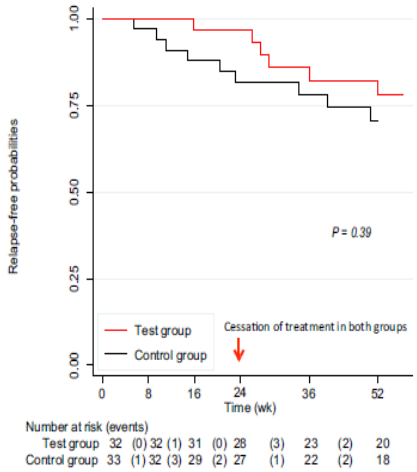
Fifty-eight patients were randomly assigned in each group without significant differences regarding baseline characteristics

Remy KI 2018

Initial treatment for MCD in adults : Alternative first line treatment

Table 2 | Primary and secondary outcomes

	Total	Test group (N = 57)	Control group (N = 57)	P value[a]	P value[b]
Primary outcome, Week 4					
Complete remission, *ITT analysis*[c]	70 (61.4)	37 (64.9)	33 (57.9)	0.44	
Remission status (without data imputation)	**109**	**52**	**57**		
Complete remission	65 (59.6)	32 (61.5)	33 (57.9)	0.70	
No complete remission	44 (40.4)	20 (38.5)	24 (42.1)		
Partial remission	10 (9.2)	4 (7.7)	6 (10.5)		0.87
No remission	31 (28.4)	14 (26.9)	17 (29.8)		
Not specified[e]	3 (2.8)	*2 (3.9)*	*1 (1.8)*		
Secondary outcomes[d]					
Week 8	**96**	**46**	**50**		
Complete remission	73 (76.0)	38 (82.6)	35 (70.0)	0.15	
No complete remission	23 (24.0)	8 (17.4)	15 (30.0)		
Partial remission	12 (12.5)	3 (6.5)	9 (18.0)		0.22
No remission	11 (11.5)	5 (10.9)	6 (12.0)		
Week 24	**90**	**46**	**44**		
Complete remission	72 (80.0)	37 (80.4)	35 (79.6)	0.92	
No complete remission	18 (20.0)	9 (19.6)	9 (20.4)		
Partial remission	7 (7.8)	2 (4.4)	5 (11.4)		0.16
No remission	9 (10.0)	7 (15.2)	2 (4.5)		
Not specified[e]	2 (2.2)	*0 (0)*	*2 (4.5)*		
Week 52	**78**	**40**	**38**		
Complete remission	57 (73.1)	27 (67.5)	30 (78.9)	0.26	
No complete remission	21 (26.9)	13 (32.5)	8 (21.1)		
Partial remission	5 (6.4)	3 (7.5)	2 (5.3)		0.72
No remission	14 (17.9)	8 (20.0)	6 (15.8)		
Not specified[e]	2 (2.6)	*2 (5.0)*	*0 (0)*		



23.1% of relapses among patients with CR at 4 weeks

Figure 3 | Relapse-free survival among the 65 patients in complete remission at 4 weeks. Relapse occurred in 15 of 65 patients who were in complete remission at week 4. One relapse occurred between weeks 4 and 8 in the control group, at the time of weaning off steroids, and 6 relapses occurred between weeks 8 and 24. Eight of the 15 relapses occurred after definitive treatment cessation (between 24 and 52 weeks of follow-up).

Remy KI 2018

Initial treatment for MCD in adults : Alternative first line treatment

Steroid sparing option with Tacrolimus and low dose of steroids

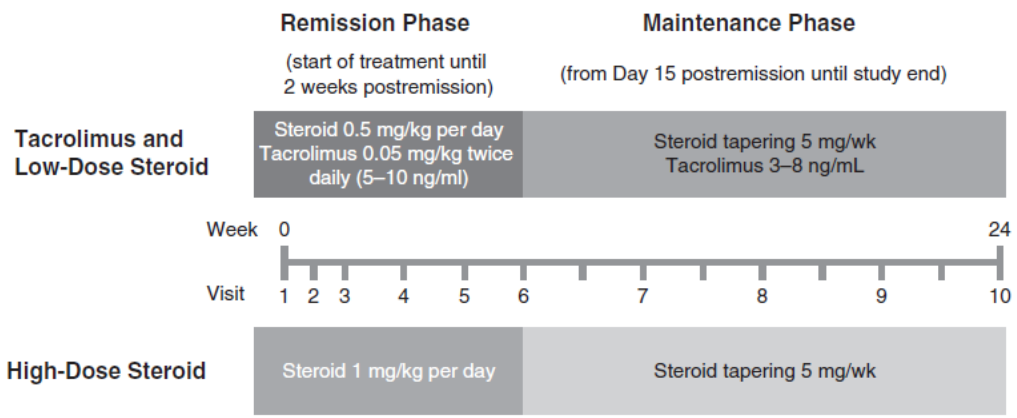


Table 1. Baseline characteristics of adult patients with MCNS in each treatment group (modified ITT)

Patient Characteristics	Tacrolimus and Low-Dose Steroid (*n*=67)	High-Dose Steroid (*n*=69)
Sex, men, *n* (%)	45 (67.2)	40 (58.0)
Age, yr	41.8±16.7	42.2±17.8
Serum albumin, g/dl	2.3±0.7	2.4±0.8
Median (min, max)	2.2 (1.1, 4.0)	2.3 (0.9, 4.1)
(95% CI)	(2.2 to 2.5)	(2.3 to 2.6)
UPCR, g protein/g creatinine	8.4±3.9	9.2±6.5
Median (min, max)	7.58 (3.3, 20.0)	7.8 (1.1, 34.8)
(95% CI)	(7.4 to 9.3)	(7.6 to 10.7)
MCNS first presentation/ relapse, *n*	32/35	36/33

Table 2. Complete remission rates and relapse after complete remission to within 24 weeks after study drug initiation, by study group (modified ITT and PPS)

Parameter	Tacrolimus and Low-Dose Steroid	High-Dose Steroid	*P* value
Modified ITT set			
Patients who showed complete remission within 8 wk after study drug initiation, *n* (%)	53/67 (79.1)	53/69 (76.8)	
Patients who showed relapse after complete remission to within 24 wk after study drug initiation, *n* (%)	3/53 (5.7)	12/53 (22.6)	0.01[a]

Chin JASN 2021

Initial treatment for MCD in adults : Alternative first line treatment

Steroid sparing regimen with Tacrolimus but without steroids

N= 50

25 Tacrolimus 0.05mg/kg X2 day levels 6 to 8 ng/ml

During 20 W

25 steroids 1mg/kg/day max 60 mg/day during 16 W

Table 2. Primary, secondary, and exploratory outcomes

Outcome	Overall			Prednisolone			Tacrolimus			*P* Value
Primary outcome	*n*	Cohort		*n*	Cohort		*n*	Cohort		
Complete remission by 8 wk	38	50	76%	21	25	84%	17	25	68%	0.32 (0.54)
Secondary outcomes	*n*	Cohort		*n*	Cohort		*n*	Cohort		
Complete remission by 16 wk	42	50	84%	23	25	92%	19	25	76%	0.25 (0.54)
Complete remission by 26 wk	45	50	90%	23	25	92%	22	25	88%	0.99 (1.00)
Any relapse after complete remission	33	45	73%	17	23	74%	16	22	73%	0.99
Exploratory outcomes	*n*	Median	Range	*n*	Median	Range	*n*	Median	Range	
Change in serum creatinine at 12 mo, mg/dl	50	0.02	−1.25 to 0.64	25	0.01	−1.25 to 0.20	25	0.02	−0.47 to 0.64	0.16
	n	Cohort		*n*	Cohort		*n*	Cohort		
Complete remission by 4 wk	22	50	44%	16	25	64%	6	25	24%	0.01 (0.05)
Complete or partial remission by 4 wk	39	50	78%	20	25	80%	19	25	76%	0.99 (1.00)
Failed to achieve complete remission	5	50	10%	2	25	8%	3	25	12%	0.99

Adjusted *P* values for multiple analyses are shown in parentheses.

Relapses 17/23 (steroid) and 16/22 (tacro) p =0.99 follow-up 78 W

Medjeral- Thomas CJASN 2020

Initial treatment for MCD in adults : Alternative first line treatment

Steroid sparing regimen : Exclusive anti CD20 therapy

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 48), pp: 28799-28804

Research Paper: Immunology

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

Roberta Fenoglio[1], Savino Sciascia[1,2], Giulietta Beltrame[1], Paola Mesiano[1], Michela Ferro[1], Giacomo Quattrocchio[1], Elisa Menegatti[2] and Dario Roccatello[1,2]

carefully ruled out. All patients received RTX as first line-therapy, without the association of corticosteroids or any other immunosuppressive agents. All the patients were treatment naive. They were treated with 4 doses of 375 mg/m^2 RTX with a 1-week interval. All patients had definite contraindications to steroid therapy (diabetes, BMI > 30, psychosis). All patients had a nephrotic

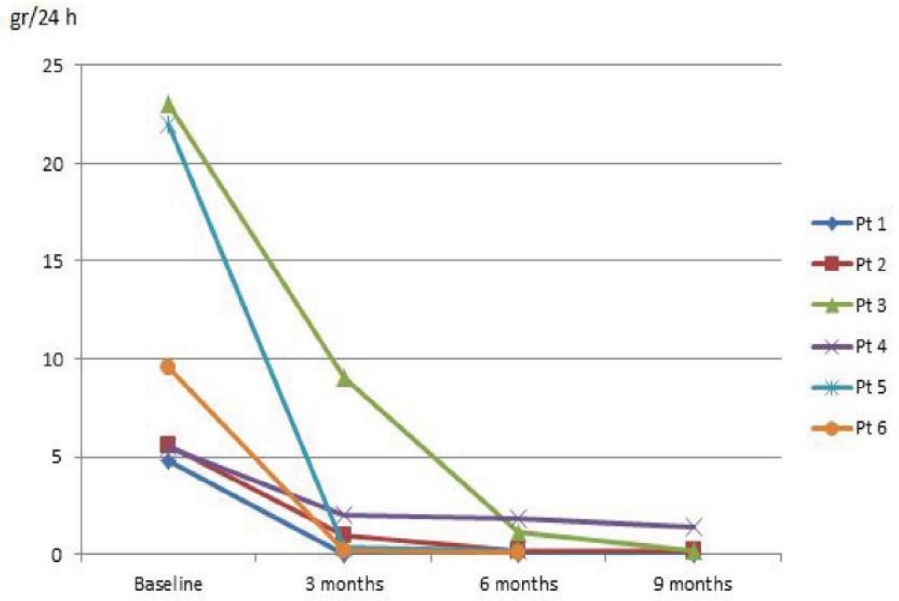


Figure 1: Evolution of proteinuria.

International recommendations

Recommendation 5.3.1. We recommend high-dose oral corticosteroids for initial treatment of MCD *(1C)*.

Practice Point 5.3.2. High-dose corticosteroid treatment for MCD should be given for no longer than 16 weeks.

KDIGO CLINICAL PRACTICE GUIDELINE
ON GLOMERULAR DISEASES

24 semaines au total

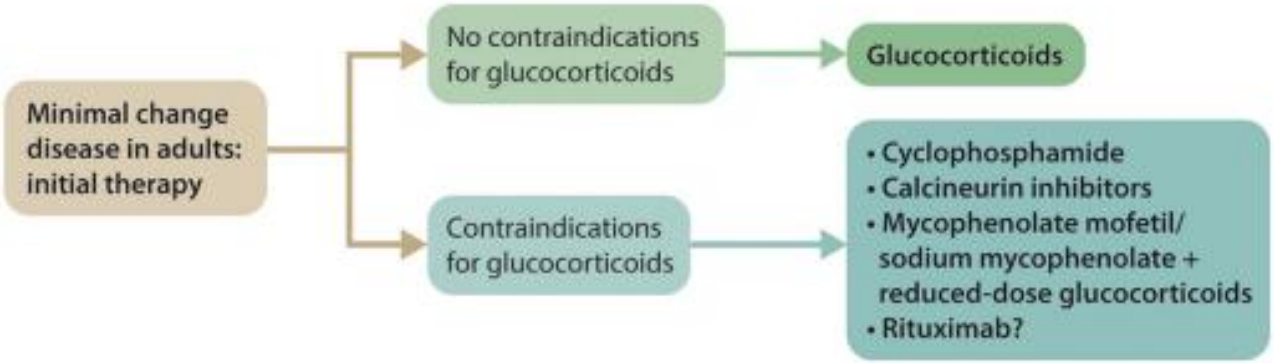


Figure 10 | Initial treatment of MCD in adults. The optimal glucocorticoid regimen is not well defined; however, suggested doses are outlined in Figure 45 of the full guideline. The choice of medication should be based on physician and patient preference. MCD, minimal change disease.

5.2. Prognosis

Practice Point 5.2.1. Long-term kidney survival is excellent in MCD patients who respond to corticosteroids, but less certain for patients who do not respond.

International recommendations

Practice Point 5.3.2. High-dose corticosteroid treatment for MCD should be given for no longer than 16 weeks.

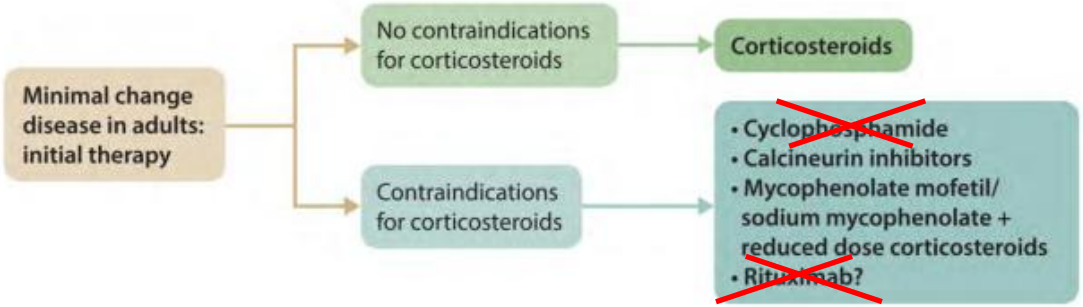
Practice Point 5.3.3. Begin tapering of corticosteroids two weeks after remission.

The optimal corticosteroid taper protocol after remission in adults is not known.

Medication	Regimen	Remission rates (complete and partial)
Initial episode, corticosteroid treatment		
Prednisone or prednisolone	Dose: 1 mg/kg per day (maximum 80 mg/day) or 2 mg/kg every other day (maximum 120 mg every other day), for a minimum of 4 weeks, and a maximum of 16 weeks (as tolerated). After remission, taper over at least 24 weeks	80%–90%
Initial episode with contraindication to corticosteroids		
Oral cyclophosphamide	2–2.5 mg/kg per day for 8 weeks	75%
Cyclosporine	3–5 mg/kg per day in divided doses for 1–2 years	75%
Tacrolimus	0.05–0.1 mg/kg per day in divided doses for 1–2 years	90%*

French recommendations (PNDS)

*Figure MCD1. Initial treatment of MCD in adults**



*The optimal corticosteroid regimen is not well-defined; however, suggested doses are outlined in Table MCD1

1. Steroids 1mg/kg/day
CR 57,9% W4
CR 70 to 84% W8

HAS
HAUTE AUTORITÉ DE SANTÉ

2. IV in cases of acute complications or severe abdominal pains

3. Total duration 24 W in adults : but possibly shorter (children PNDS and international recommendation total 2240 mg/m2 for 8 W)

4. Contraindications or risk of side effects (24 W of treatment)

- ***Low dose 0.5 mg/kg/jr + MMF***
- ***Tacrolimus alone***
- ***Low dose 0,5mg/kg/day + Tacrolimus***

Remy et al KI 2018 ***Medjeral- Thomas CJASN 2020*** ***Chin JASN 2021***

Frequently relapsing/ steroid dependent MCD

Steroid dependant
- **14 à 30%**

Frequent relapses (two or more relapses per 6 M)
- **11 à 29%**

Hogan J JASN 2013

Cyclophosphamide / MMF

(**Observational study**)

22 patients **Cyclophosphamide SNDS FRNS**
2-2,5 mg/kg/jr during 8 W

CR 86% (at one year) 74% (at 3 years) and 63% (at 5 years)

Mak NDT 1996

(**Observational study**)

20 patients **Cyclophosphamide**
During 11,5W

CR 55%
CR 80% for **SDNS** et 50% for **FRNS**

(**Observational study**)

29 patients **MMF** Mean follow-up 32M
CR 86%

Sandoval CKJ 2017

10 patients **MMF**
CR 65%
Relapses 35%

Waldman M CJASN 2007

Frequently relapsing/ steroid dependent MCD

Cyclosporine/ Tacrolimus

(Multicenter randomized controlled trial)

73 patients (11 adults *62 children*)
MCD = 31 **SDNS/FRNS**
Cyclophosphamide 2,5mg/kg/day (8W)
vs
Csa 5 mg/kg/mois (9M)

M9 p=NS
CR 64% **Cyclophosphamide**
CR 74% **Csa**

Relapse at M24
75% (**Csa**) **>** 37%
(**Cyclophosphamide**)

Ponticelli NDT 1993

(Prospective cohort)

26 patients **SDNS** adults
N =14 **Cyclophosphamide** IV 750 mg /4 W during 24 W

N= 12 **Tacro** during (24 W)

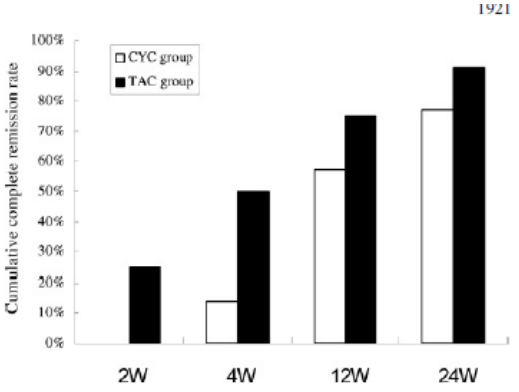


Fig. 1. Cumulative CR rates in patients receiving CYC or TAC. Although the rate of CR was not significantly different between the two groups at the end of 24 weeks therapy, the tendency of higher rate of CR was seen more often in the TAC group than CYC group before 4 weeks treatment.

CR **Tacro** 90,9% / **Cyclophosphamide** 76.9% à W24 NS
Relapses **Tacro** 50 % **Cyclophosphamide** 40% NS

Li NDT 2008

Frequently relapsing/ steroid dependent MCD

Rituximab a new therapeutic relevant option in children

Prospective randomized controled trial

- **SDNS**

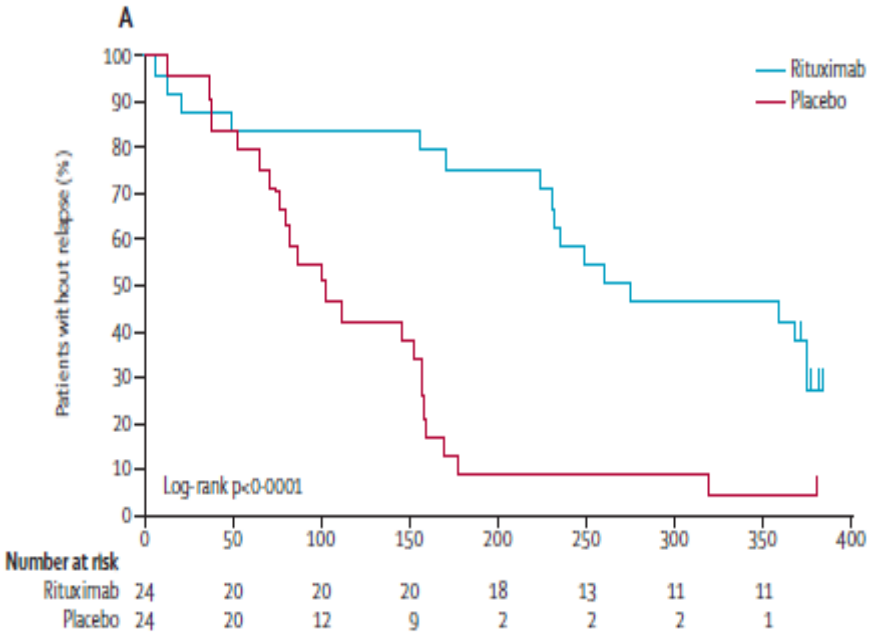
24 patients Ritux (4 X 375mg/m2) et 24 placebo

Delay without relapses 267 days jrs vs 101days p<0,001)

	Number of patients*	Daily prednisolone dose in the 365 days before randomisation (mg/m² per day)	Daily prednisolone dose after randomisation (mg/m² per day)	p value
Rituximab	19	19·13 (9·94)	8·37 (5·62)	<0·0001
Placebo	21	18·02 (10·15)	21·02 (9·81)	0·21

Data are mean (SD), unless otherwise stated. *Number of patients in each group for whom prednisolone doses were available for 365 days before randomisation.

Table 3: **Change in daily prednisolone dose before and after randomisation, by group**



Ijima Lancet 2014

Frequently relapsing/ steroid dependent MCD
Rituximab a new therapeutic promising option in adults

1) **Retrospective study**

17 patients Mean age 29,4 y 10 patients traités en RC

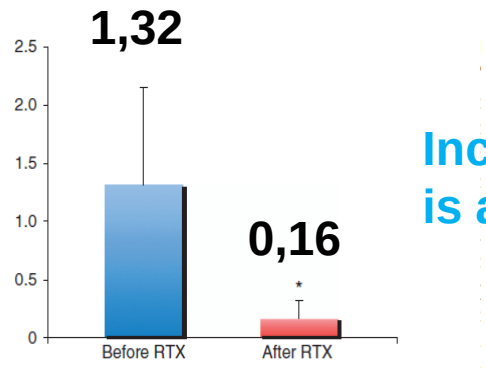


Figure 1 | Number of relapses per year before and after rituximab treatment (*$P < 0.05$). Results are the mean ± s.d.

❖ **SDNS**

Incidence of relapses lower 20% vs 57% when Ritux is administered in patients with CR

Munyentwali H KI 2013

2) **Retrospective study**

16 patients avec SNLGM
(13 SDNS, 2 FRNS 1 SRNS)
Median follow-up 44 mois

13 patients treated in CR

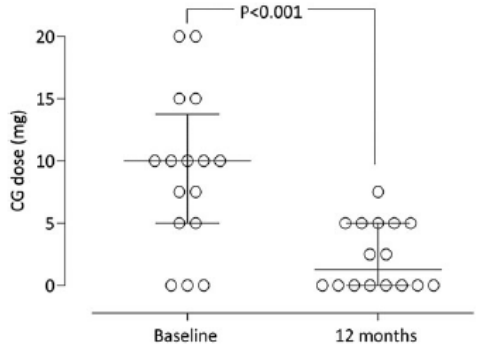


FIGURE 1. Lowest glucorticoid (GC mg) dose before relapse (baseline) and GC dose at 12 months.

Bruchfeld A NDT 2013

3) **Observational sudy)**

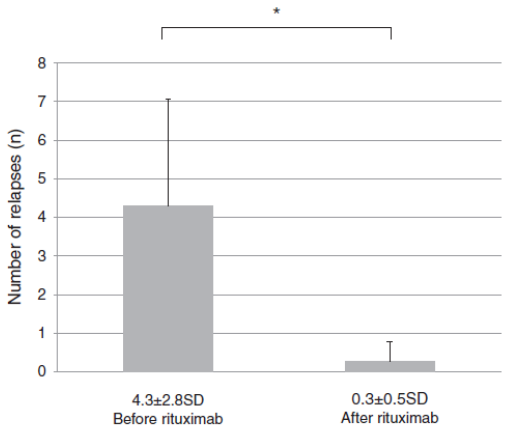


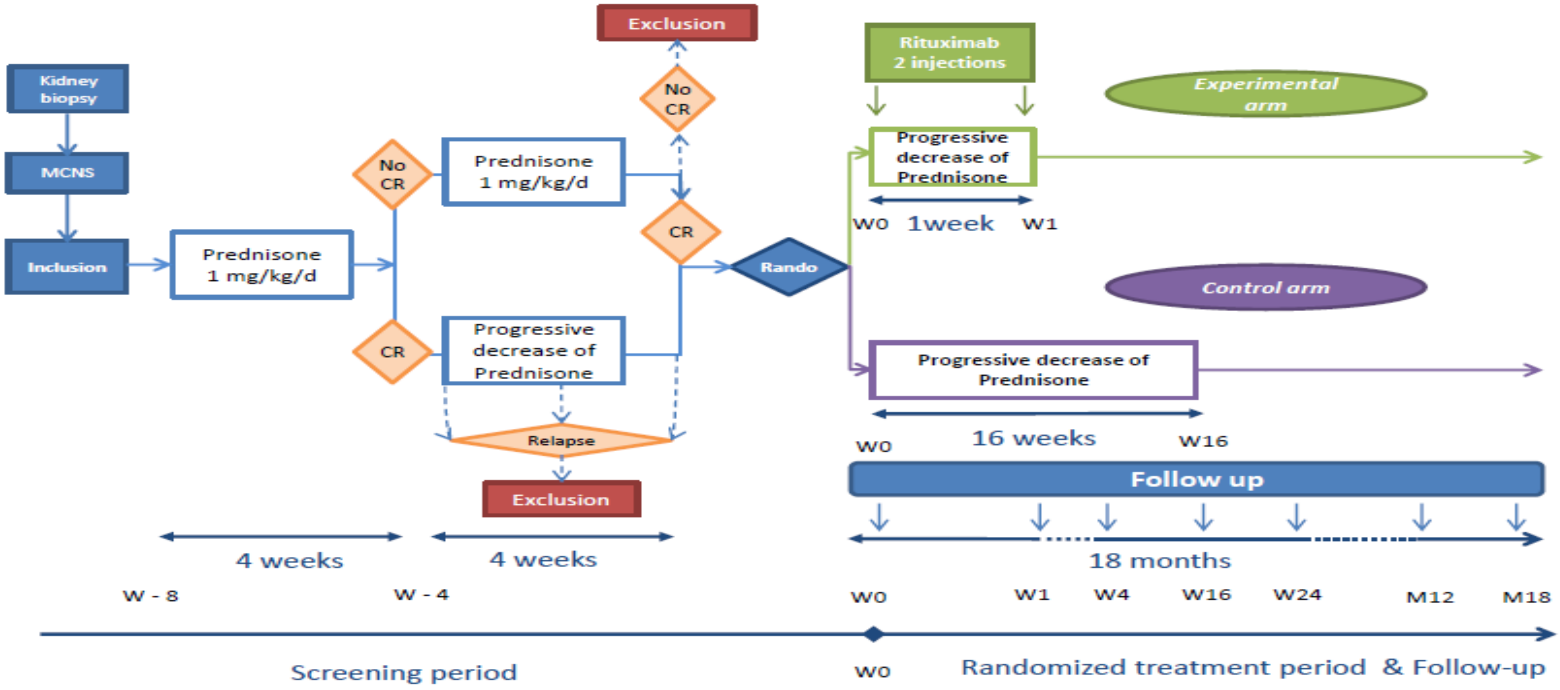
FIGURE 2. Number of relapses during the 24-month period before and 24-month period after the 1st rituximab administration. Results are expressed as means ± S.D. *$P < 0.05$.

Iwabuchi Y Medicine 2014

Frequently relapsing/ steroid dependent MCD

In the future : early use of Rituximab to prevent subsequent relapses ?

phase IIb, randomized, open-label, parallel group, in a 1:1 ratio, active controlled, multicenter trial testing the efficacy and safety of two injections of Rituximab separated by one week 375mg/m2 compared to the standard regimen of oral steroid alone (progressively tapered within 24 weeks) from initial episode of MCD in adults.



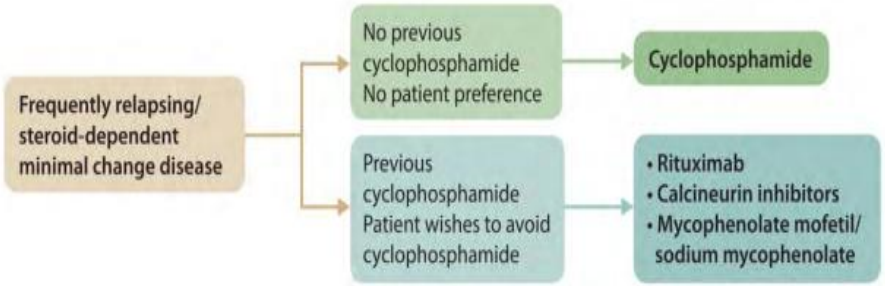
The primary endpoint will be the incidence of MCD relapse during the 12 months following randomization

PHRC PI : Audard V

International recommendations

Practice Point 5.3.1.1. Algorithm for treatment of frequently-relapsing/steroid-dependent MCD in adults (Figure MCD2)

Figure MCD2. Treatment of FR/SD MCD in adults



Recommendation 5.3.1.1. We recommend cyclophosphamide, rituximab, calcineurin inhibitors, or mycophenolic acid analogs (MPAA) for the treatment of frequently-relapsing/corticosteroid-dependent MCD as compared to prednisone alone or no treatment *(1C)*.

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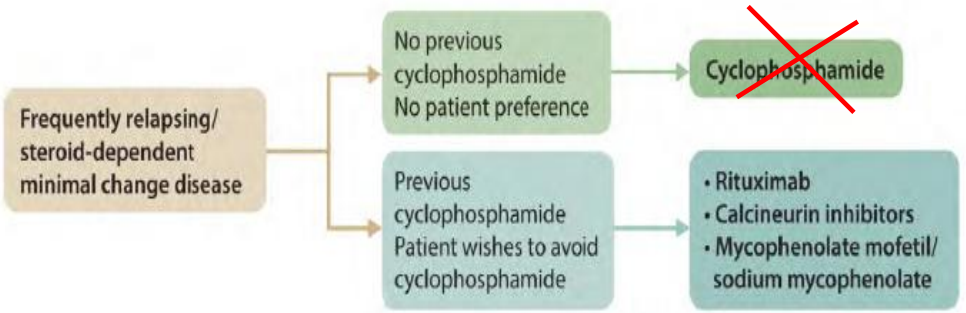
Frequently relapsing/ steroid-dependent patients		
Oral cyclophosphamide	2–2.5 mg/kg/day, adjusted for white blood counts, for 8–12 weeks. 12 weeks may be associated with less relapse in steroid-dependent MCD	75%
Calcineurin inhibitors • Cyclosporine • Tacrolimus	**Initial dose:** 3–5 mg/kg per day in divided doses for 1–2 years 0.05–0.1 mg/kg per day in divided doses for 1–2 years • If serum levels are being monitored, suggested initial levels: - Cyclosporine: 150–200 ng/ml - Tacrolimus: 4–7 ng/ml • After withdrawal of corticosteroids reduce CNI dose if possible Suggested doses: <3mg/kg/day for cyclosporine and <0.05 mg/kg/day for tacrolimus • Attempt gradual taper and discontinuation of CNI after a minimum of one year of therapy if possible • If CNI-dependent reduce dose to lowest possible to maintain remission with monitoring of kidney function (kidney biopsy if kidney dysfunction) Switch to alternate medication if evidence of CNI toxicity	70–90% 90%
Rituximab	**Induction regimens:** • 375 mg/m² weekly for 4 doses • 375 mg/m² × single dose; repeat after one week if CD19 cells >5/mm³ • 1 g/dose for 2 doses, 2 weeks apart **Relapse after induction:** • 375mg/m² × 1 dose or • 1g i.v. × 1 dose	70% (20% off all immunosuppression, 50% on one other immunosuppressive drug)
Mycophenolic acid analogues • Mycophenolate mofetil • Sodium mycophenolate	**Initial dose:** 1000 mg twice daily 720 mg twice daily • Attempt gradual taper and discontinuation of mycophenolic acid analogues after a minimum of one year of therapy if possible	

French Recommendations

KDIGO CLINICAL PRACTICE GUIDELINE
ON GLOMERULAR DISEASES

Practice Point 5.3.1.1. Algorithm for treatment of frequently-relapsing/steroid-dependent MCD in adults (Figure MCD2)

Figure MCD2. Treatment of FR/SD MCD in adults



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First line MMF
500-1000 mg twice daily

For 1-2 years

second line CNI
CSA: 3-5 mg/kg/d starting dose
TAC: 0.05-0.1 mg/kg/d start

Following 3 months of stable remission. Tapering to minimum required dosage, for 1-2 years

Fisrt line Rituximab

Initial dosing
- Single-dose: 1g or 375 mg/m²
- or
- 2x 1g fixed-dose, 2 weeks apart

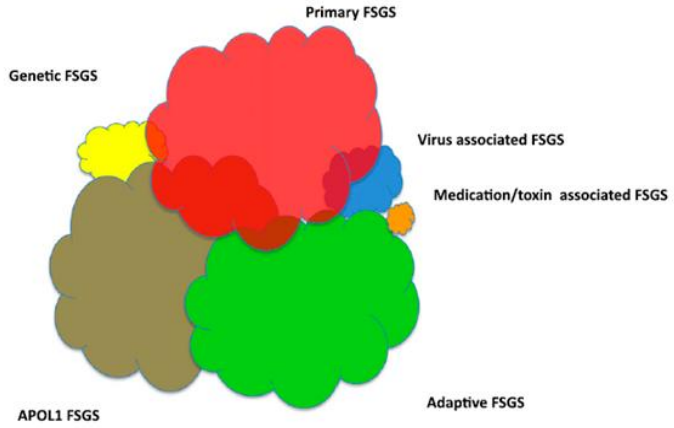
Wait & expect response for 4-6 months

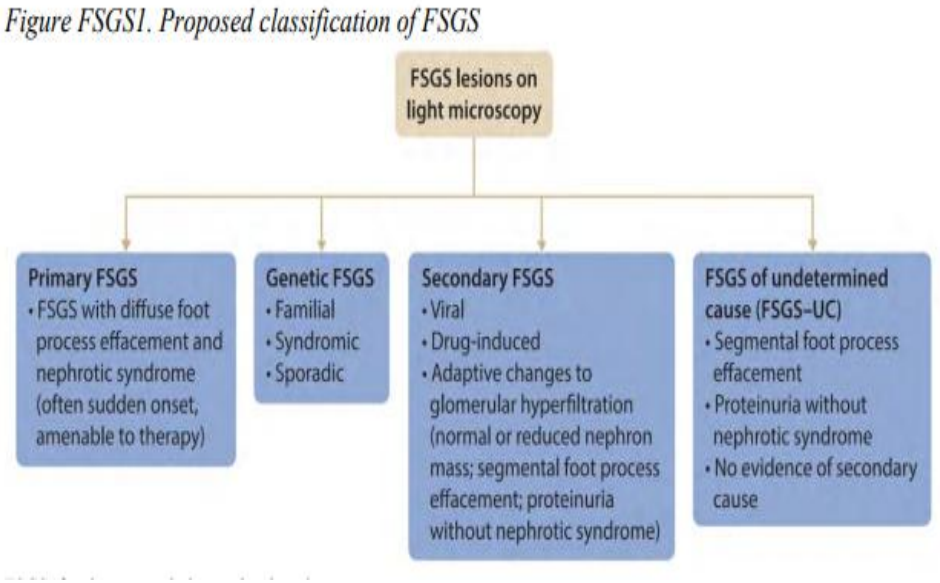
Subsequent dosing
- Single-dose (1g / 500 mg)
- or
- Fixed-/Tailored-interval (e.g. 4-6 months intervals, tailored according to relapse history)
- Clinically-driven (e.g. proteinuria and/or CD19 monitoring)

Stop RTX after 24 months of remission and continue monitoring.

Treatment of primary FSGS in adults

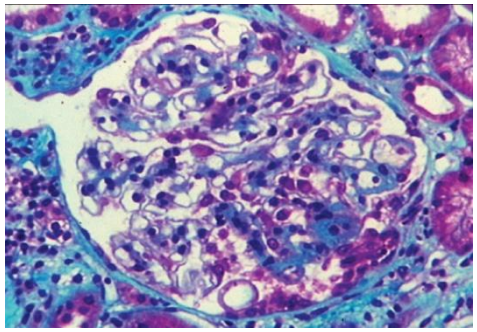
First challenge : differentiate primary from secondray forms of FSGS

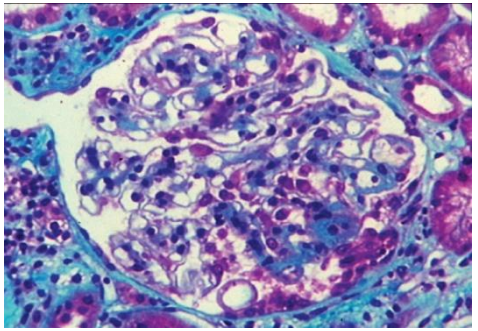




Rosenberg CJASN 2017

De Vriese Nature Reviews Nephrol 2021





Patients with FSGS lesion on renal biopsy : steroids and/imunusuppressive drugs versus supportive therapy

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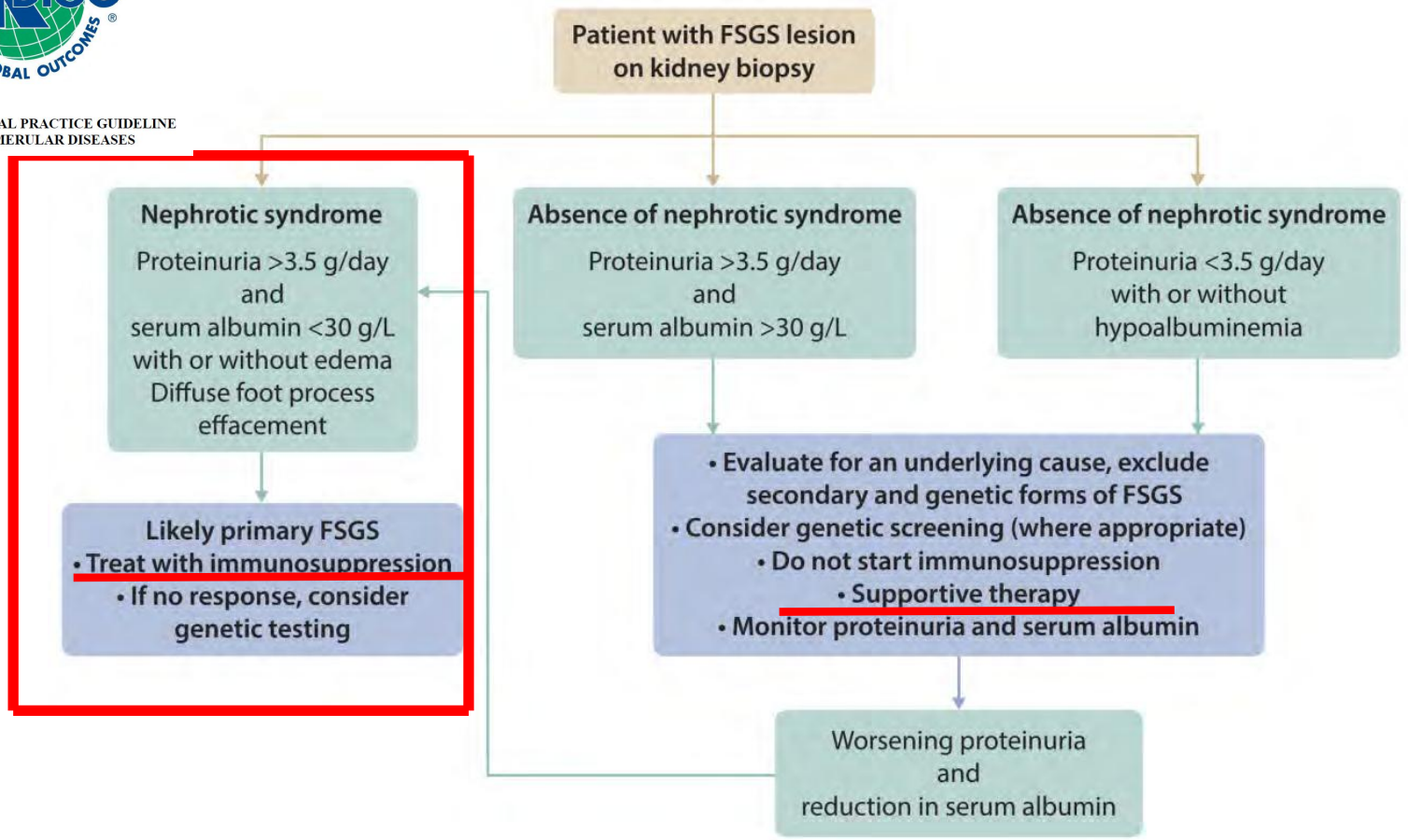

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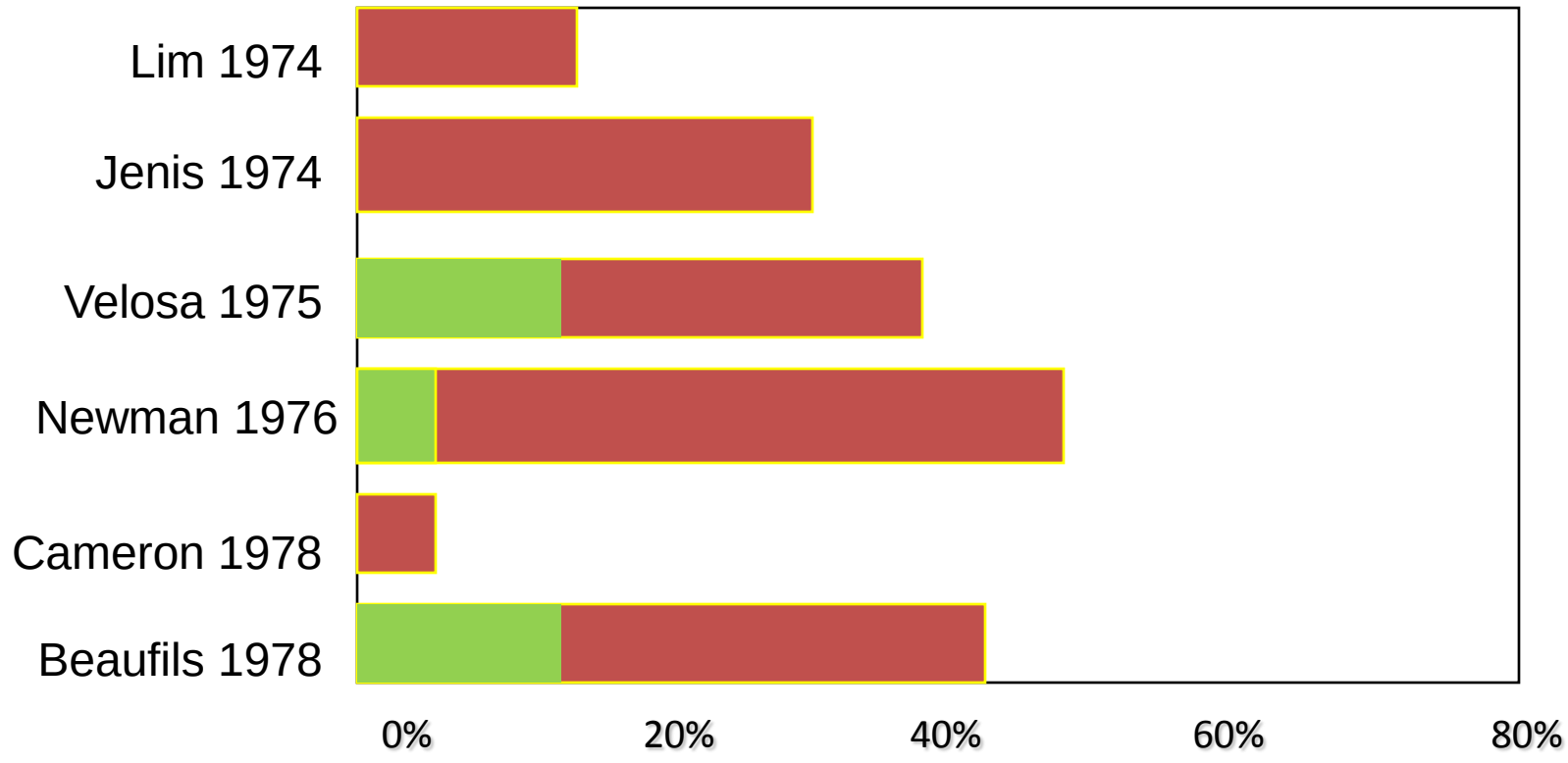
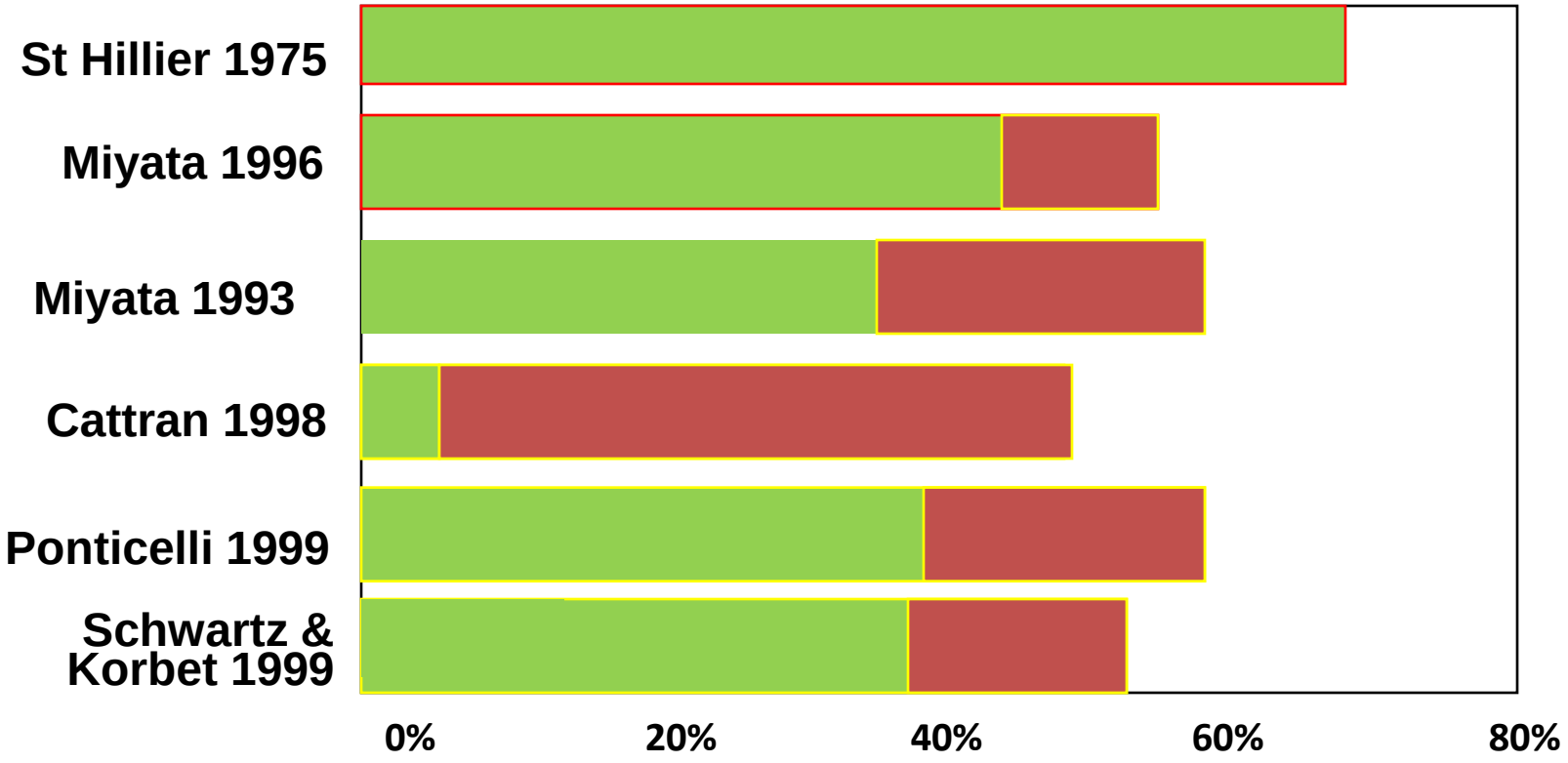
Response with low dose of steroids



Remission: Complete Partial

Response with high doses of steroids



Steroids : Optimal duration of steroids therapy is not known

Duration	Complete Rémission rate
≤ 16 weeks	15 %
> 16 weeks	61 %

Ponticelli AJKD 1999

Définition of steroid resistance : 1 mg/kg during 16 weeks

Remission 47 à 66% (CR 32 à 47% and PR 19 à 29%)

Korbet JASN 2012

International recommendations

KDIGO CLINICAL PRACTICE GUIDELINE
ON GLOMERULAR DISEASES

6.2.2. Initial treatment of primary FSGS

Recommendation 6.2.2.1. We recommend that high-dose oral corticosteroids be used as the first-line immunosuppressive treatment for primary FSGS *(1D)*.

Practice Point 6.2.2.2. Initial high-dose corticosteroids should be continued until complete remission is achieved or as tolerated by patients up to a maximum of 16 weeks, whichever is earlier.

Practice Point 6.2.2.3. Adults with primary FSGS who respond to corticosteroid treatment should receive corticosteroids for at least six months.

International recommendations

Practice Point 6.2.2.4. In adults with relative contraindications or intolerance to corticosteroids, alternative immunosuppression with calcineurin-inhibitors should be considered as the initial therapy in patients with primary FSGS (Table FSGS4).

Calcineurin inhibitors	**Starting dose:** • Cyclosporine 3–5 mg/kg/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated

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Cyclosporine 3mg/kg/jr AND steroids 0,5 mg/kg/jr during 3 mois
VS
steroids 1mg/kg/jr from 3 to 6 M

Retrospective study

- Remission 87,7% % vs 62,5% (NS)

Goumenos Nephron Clin Pract 2006

MMF 1gr X 2 /jr AND steroids 0,5 mg/kg/jr during 6 M (n=17)
VS
Steroids 1mg/kg/jr from 3 to 6 mois (n=16)

Prospective study

- Remission 70% vs 69% (NS)
- Delay 6 W vs 10 W(NS)
- Relapse 23% vs 18% (NS)

Senthil Nayagam NDT 2008

Steroid resistant FSGS

40 à 60 % of cases

Ciclosporine A

49 adults

- 26 csa (3,5 mg/kg/jr)
- 23 placebo

During 6 mois

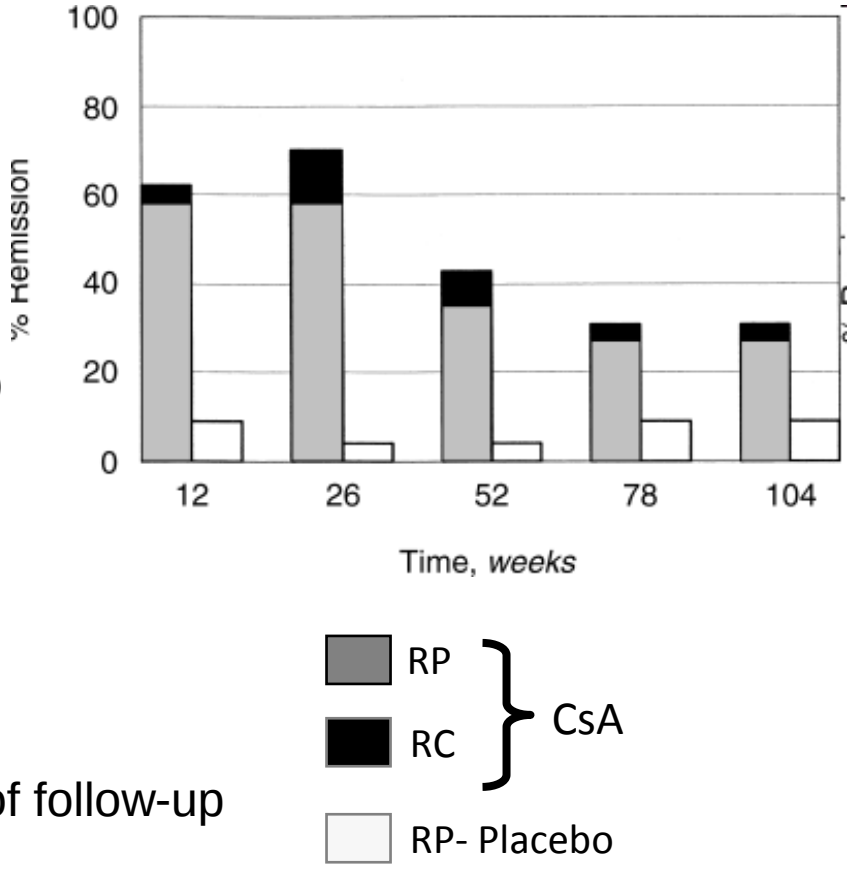
In association with low dose of steroids (0,15mg/kg/jr)

Remission at 6M 69% (CR 12% et PR 57%)

placebo remission (4%)

Mean delay of remission 7 W (1 to 25)

Major concern 60% of relapses after 78 W of follow-up



W26 $P < 0.001$ à W104 $P < 0.05$.

Cattran D KI 1999

6.3. Special situations

6.3.1. Corticosteroid-resistant primary FSGS

Recommendation 6.3.1.1. For adults with corticosteroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for at least six months rather than continuing with corticosteroid monotherapy or not treating *(1C)*.

Practice Point 6.3.3.1. Adults with corticosteroid-resistant primary FSGS who respond to CNI treatment should receive CNIs for a minimum of 12 months to minimize the risk of relapses (Table FSGS5).

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Treatment of steroid resistance and resistance to CNI

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Identifying a potential associated genetic diagnosis

- Major therapeutic implcations
- Immunusuppressive agents should not be continued in patients with monogenic SRND
- ✓ **Primary versus secondray forms of FSGS (intial exstensive screening for a secondary cause ?)**
- ✓ **FSGS in patient from African ancistry**
- Polymorphisms in the gene for apolipoprotein L1 (APOL1) should be investigated
- Successful use of steroids and immunosuppressive drugs in these patients remains to be determined

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Treatment of steroid resistance and resistance to CNI

➢ A place for Rituximab therapy ?

If patients have not responded to glucocorticoids or a CNI, the therapeutic choices for primary FSGS are limited

Table 2
Overview of studies of rituximab in minimal change disease and focal segmental glomerulosclerosis in adults.

First author, (study)	Year	Design	Patients	RTX / Immunosuppression	FU	Proteinuria	Relapse
Bruchfeld [103]	2014	Retrospective	16 adults, SD/SR/FR MCD	RTX (different regimes) + CS +/− RTX re-application	44 months (median, 12–17)	Initial CR ± PR: 93.8% CR ± PR at end of FU: 50%	RR at end of FU: 43.8%
Munyentwali [93]	2013	Retrospective	17 adults, SD/FR MCD	RTX (different regimes) +/− RTX re-application	29.5 months (median, 5.1–82)		RR: 39%; Reduction of RR per year: from 1.32 +/− 0.85 before to 0.16 +/− 0.21 after RTX ($p < 0.05$)
Ruggenenti, (NEMO) [92]	2014	Prospective, multicenter, off-on	10 children, 20 adults, SD/FR MCD, MesGN, FSGS	RTX (single-dose or 2 × 375 mg/m^2)	12 months before and after RTX		Number of relapses: 22 after RTX versus 88 before RTX RR after RTX: 70% in children versus 40% in adults 54.5% in MCD/MesGn versus 37.5% in FSGS
DaSilva [94]	2017	Retrospective, multicenter (GLOSEN registry)	28 (RTX) + 22 (control) adults, SD/FR MCD/MesGN ($n = 42$) / FSGS ($n = 8$)	CS + additional IS +/− RTX		CR: 82% (RTX) versus 63% (control)	Reduction of RR per year: 1.1 +/− 0.63 versus 0.01 +/− 0.02 ($p < 0.0001$) RR after RTX: FSGS > MCD ($p = 0.02$)
Guitard [95]	2014	Retrospective, multicentre	41 adults, SD/FR MCD	RTX (different regimes) +/− RTX re-application +/− additional IS	39 months (median, 6–71)	CR: 61%, PR: 17%	RR: 56% of responders; median time to relapse: 18 months (3–36)
Roccatello [96]	2017	Prospective	8 adults, FSGS (complex)	High-dose RTX (8 weekly 375 mg/m^2)	29.1 months (median, 24–42)	Non-significant reduction from 5.3 ± 1.9 g/day before to 3.9 +/− 1.8 g/day after RTX	
Fernandez-Fresnedo [97]	2009	Retrospective, multicenter (GLOSEN registry)	8 adults, SR FSGS	RTX (different regimes) +/− re-applications; several IS prior and concomitant to RTX	16.4 months (mean, 12–24)	Non-significant reduction from 14.0 +/− 4.4 g/d before to 10.5 +/− 4.9 g/d after RTX	
Colliou [104]	2019	Retrospective, multicentre	23 adults (≥ 60 years), MCD/FSGS; (out of 116 total)	RTX alone (n = 1), + CS ($n = 21$), + CNI ($n = 1$)	34 months (median, 11.8–56.5), (total patients)	CR: 14/23 (61%), PR: 4/23 (17%)	RR: 7/23 (30%); Median time to relapse: 13 months *(no differentiation of mixed cohort possible)*
Ramachandran [98]	2019	Prospective, singlecentre; (RTX to maintain remission)	24 adults (17–48 years), SD/SR MCD ($n = 11$)/FSGS ($n = 13$) with CNI-dependence	RTX 1 × 375 mg/m^2 +/− additional low-dose (100 mg); +/− additional IS	12 months	Overall-CR: 54%, -PR: 25% MCD-CR: 100% FSGS-CR: 38%, -PR: 38% SD-CR: 93%, -PR: 7% SR-CR: 22%, -PR: 44%	RR: 8/24 (33%) Median time to relapse: 7 months

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Can be tested

Gauckler Autoimmunity Reviews 2020

Treatment of steroid resistance and resistance to CNI

➢ A place for Rituximab therapy ?

Only a minority (three of eight) of patients in our series of adult patients with FSGS showed a positive influence of rituximab.

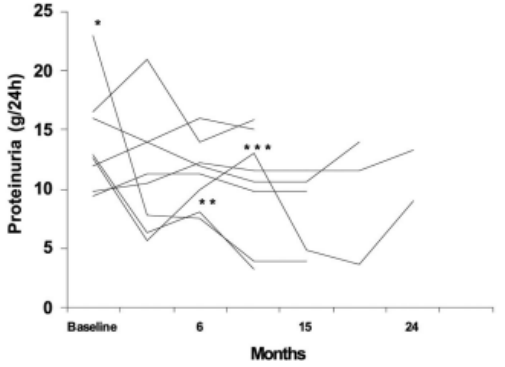

Figure 1. Evolution of proteinuria after rituximab therapy. *Patient 8 received eight weekly consecutive infusions (375 mg/m^2) of rituximab at baseline; **patient 7 received two more rituximab infusions (375 mg/m^2) at 6 mo; ***patient 6 received four more rituximab infusions (375 mg/m^2) at 12 mo.

Fernandez-Fresnedo CJASN 2009

Table 1. Demographic and clinical characteristics of the patients with FSGS treated with RTX

Patient	M/F	Age	Treatment	Baseline				Month 6				Month 12				Month 18			
				sCr	prot.	alb.	BP	sCr	prot.	alb.	BP	sCr	prot.	alb.	BP	sCr	prot.	alb.	BP
1	M	61	ACEi + ARBs	1.2	8	2.8	140/90	1.4	6.7	2.9	140/90	1.6	9.3	2.7	145/90	1.7	6.1	2.7	140/80
2	F	60	ACEi + ARBs	1.7	3.8	2.9	160/70	2	2.8	3.4	150/90	2.2	3.8	2.8	150/90	2.3	3.2	2.9	140/90
3	F	81	ACEi + ARBs	3.7	7	2.6	140/70	3.3	7	2.9	120/70	2.5	4.9	3.3	120/70	2.0	1.5	3.9	120/70
4	M	62	ACEi + ARBs + CCB	1.6	7	2.9	130/90	2.0	4.6	2.2	130/90	2.9	3.9	2.6	130/80	2.7	5.2	2.4	130/80
5	M	42	ACEi + ARBs	3.7	3.6	2.5	140/90	6.4	6.4	2.4	130/80	6.4	6	2.5	130/80	9	6.4	2.4	130/80
6	M	70	ACEi + ARBs	2.8	4	2.6	130/90	3.2	2.7	2.5	120/70	3.5	2.8	2.9	130/80	3.5	2.7	2.8	130/70
7	F	71	ACEi + ARBs	3.5	3.6	2.8	130/90	3.5	2.9	2.8	130/80	3.5	2.2	2.7	140/80	3.5	2.5	2.8	130/80
8	F	40	ARBs + CCBs	0.9	3.8	2.9	140/90	0.9	2.7	2.6	130/80	0.9	2.3	2.6	130/70	0.9	2.9	3.2	130/70

FSGS, focal segmental glomerulosclerosis; RTX, rituximab; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blocker; sCr, serum creatinine (mg/dL); prot., proteinuria (g/24 h); BP, blood pressure, mm Hg; alb., serum albumin, g/L.

Only a minority (1 of 8) in our series of adult patients with FSGS showed positive effects of high doses of RTX (8 weekly doses of 375 mg/m2)

Roccatello Am J of Nephrology 2017

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Treatment of steroid resistance and resistance to CNI

➢ A place for Apherisis ?

21 adults
FSGS 12 et MCD 9
SD-INS 9,5%
SR-INS 90,5%

Delay between initial diagnosis and apherisis onset = 10 months

Median number of apheresis sessions = 12

CR or PR 7/21 (33%)

Table 3. Parameters associated with remission (univariate analysis)

	Odds ratio	95% CI	*P* value
All patients (*n* = 21)			
Age ≥50 y	22.6	1.00–525	**0.006**
Time from diagnosis to apheresis < 12 mo	10.8	1–117	**0.043**
Change in proteinuria before apheresis > 4.5 g/d	9.17	1.15–73.2	**0.041**
Dialysis for acute kidney injury at the time of apheresis	22.0	1.00–524	**0.026**
Dialysis or change in proteinuria > 4.5 g/d before apheresis	22.0	1.86–107	**0.001**

CI, confidence interval.

Moret KI Reports 2021

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ON GLOMERULAR DISEASES

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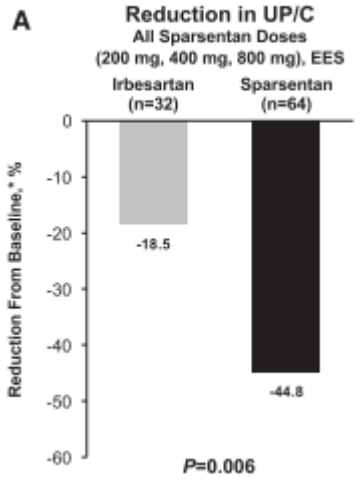
CLINICAL RESEARCH www.jasn.org

DUET: A Phase 2 Study Evaluating the Efficacy and Safety of Sparsentan in Patients with FSGS

Howard Trachtman,[1] Peter Nelson,[2] Sharon Adler,[3] Kirk N. Campbell,[4] Abanti Chaudhuri,[5] Vimal Kumar Derebail,[6] Giovanni Gambaro,[7] Loreto Gesualdo,[8] Debbie S. Gipson,[9] Jonathan Hogan,[10] Kenneth Lieberman,[11,12] Brad Marder,[13] Kevin Edward Meyers,[14,15] Esmat Mustafa,[16] Jai Radhakrishnan,[17] Tarak Srivastava,[18,19] Miganush Stepanians,[20] Vladimír Tesar,[21,22] Olga Zhdanova,[23] Radko Komers,[24] and on behalf of the DUET Study Group



Travere Therapeutics Announces Achievement of Interim Proteinuria Endpoint in the Ongoing Phase 3 DUPLEX Study of Sparsentan in Focal Segmental Glomerulosclerosis

Sparsentan achieved statistically significant response on interim proteinuria endpoint compared to irbesartan after 36-weeks of treatment

To date in the study, sparsentan has been generally well-tolerated and has shown a safety profile comparable to irbesartan

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 16, 2023 VOL. 388 NO. 11

Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

O. Egbuna, B. Zimmerman, G. Manos, A. Fortier, M.C. Chirieac, L.A. Dakin, D.J. Friedman, K. Bramham, K. Campbell, B. Knebelmann, L. Barisoni, R.J. Falk, D.S. Gipson, M.S. Lipkowitz, A. Ojo, M.E. Bunnage, M.R. Pollak, D. Altshuler, and G.M. Chertow, for the VX19-147-101 Study Group*

Table 2. Mean Percent Change from the Baseline Urinary Protein-to-Creatinine Ratio at Week 13.*

Variable	Total (N=13)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=10)
Mean urinary protein-to-creatinine ratio			
At baseline	2.21±0.95	3.47±1.07	1.84±0.52
At wk 13	1.27±0.73	1.83±0.58	1.10±0.71
Geometric percent change from baseline at wk 13 (95% CI)	−47.6 (−60.0 to −31.3)	−47.7 (−70.1 to −8.5)	−47.5 (−63.4 to −24.6)

Acknowledgments

ORKiD FILIÈRE ORPHAN KIDNEY DISEASES

RCP SNI X 1 /mois