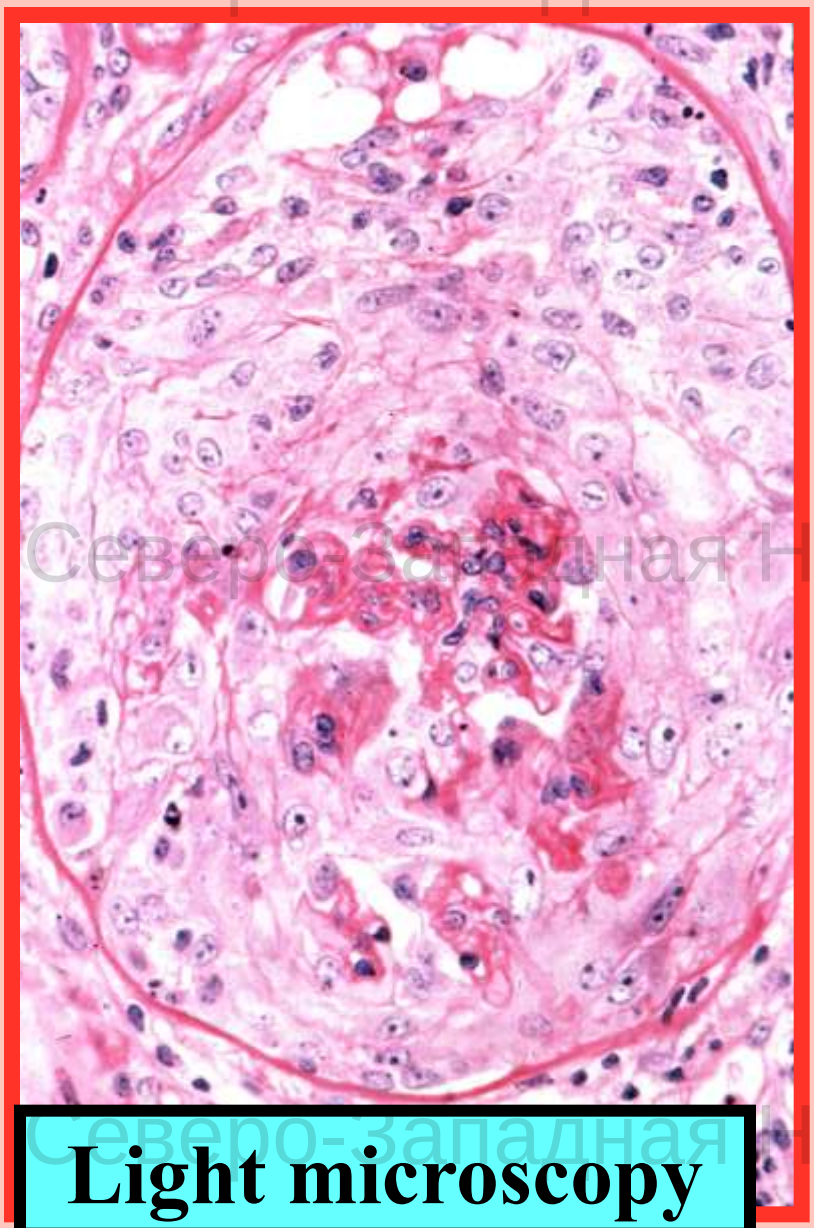
Russia Dialysis Society
Peterhof, Russia
June 8, 2016

РДО

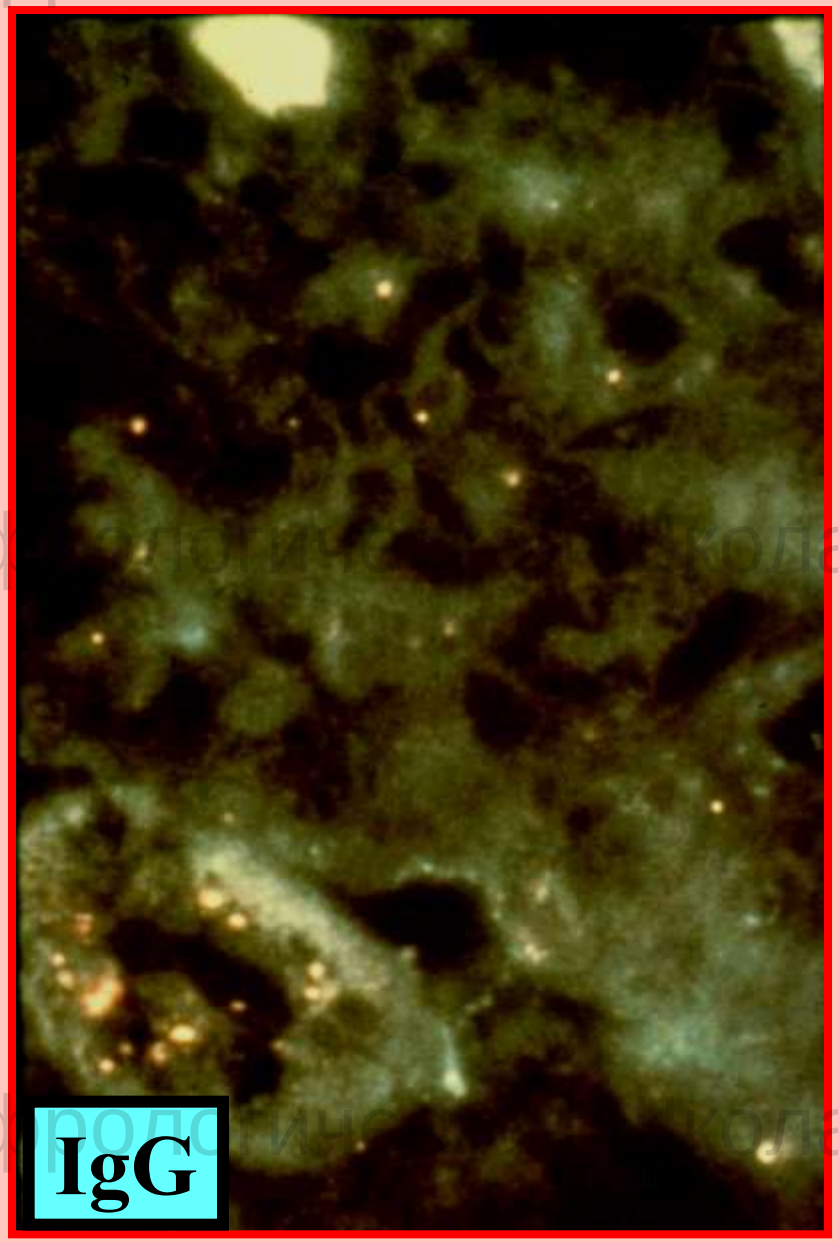
TREATMENT OF GLOMERULONEPHRITIS
(AAV, SLE, Membranous)
What's changed in the past decade?

William Couser, MD
Affiliate Professor of Medicine
University of Washington
Seattle, WA USA

ANCA-positive, “pauci-immune” crescentic GN



Light microscopy



IgG

Induction therapy in renal vasculitis

KDIGO CPG for GN (Kidney Int Suppl 2:142, 2012

Consider Rituximab induction especially when:

- **Fertility is an issue**
- **Risk of malignancy is high**
- **Patient is frequently relapsing**

Rituximab is as safe and effective as oral Cytoxan for induction in patients with AAV who have renal involvement*?
(*Post hoc* analysis of the RAVE trial (Rit X4 vs po CTX)
(*GN on biopsy, RBC casts or increased Scr due to AAV)

Follow up Time (18 mos)	Rituxan (n =51)	CTX/AZA (n=51)
Complete remission (%)	63%	76%
Time to relapse	170 days	130 days
Adverse events	30	39

Adapted from Geetha et al. JASN 26:976, 2015

What is the status of plasma exchange (PLEX) for induction in AAV in 2015?

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Maintenance therapy – AAV

(KDIGO CPG for GN (Kidney Int Suppl 2:142, 2012)

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In 2016, there is increasing anecdotal data to suggest that Rituximab may be more effective than Immuran in maintaining remission in AAV and that Rituximab might therefore be the optimal therapy for both induction and maintenance.

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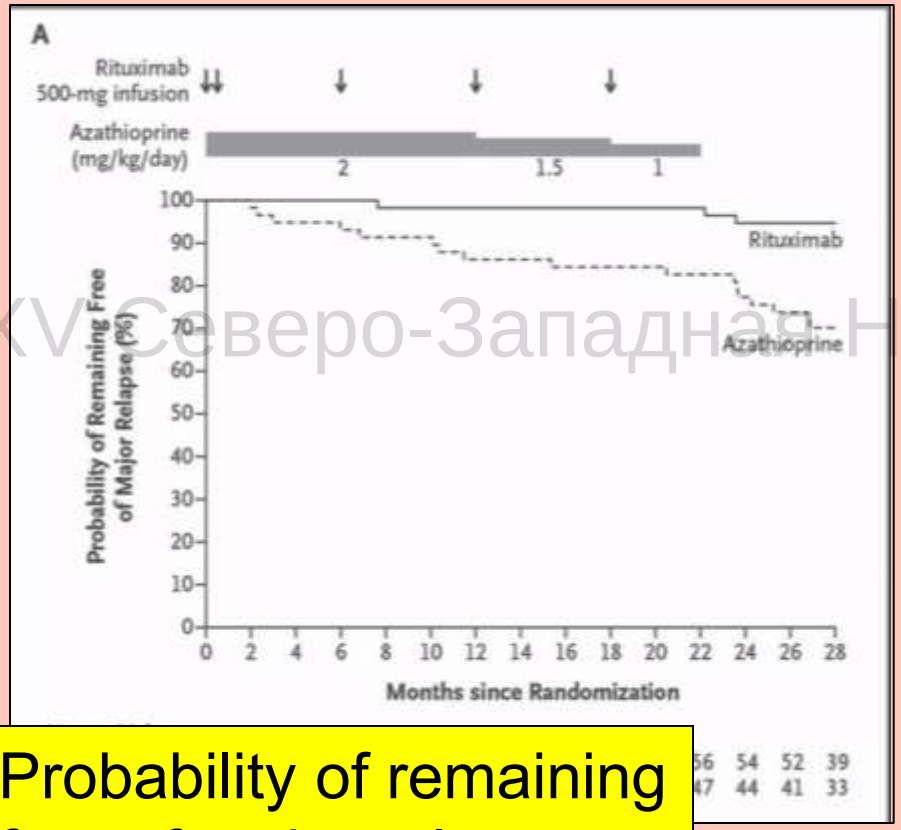
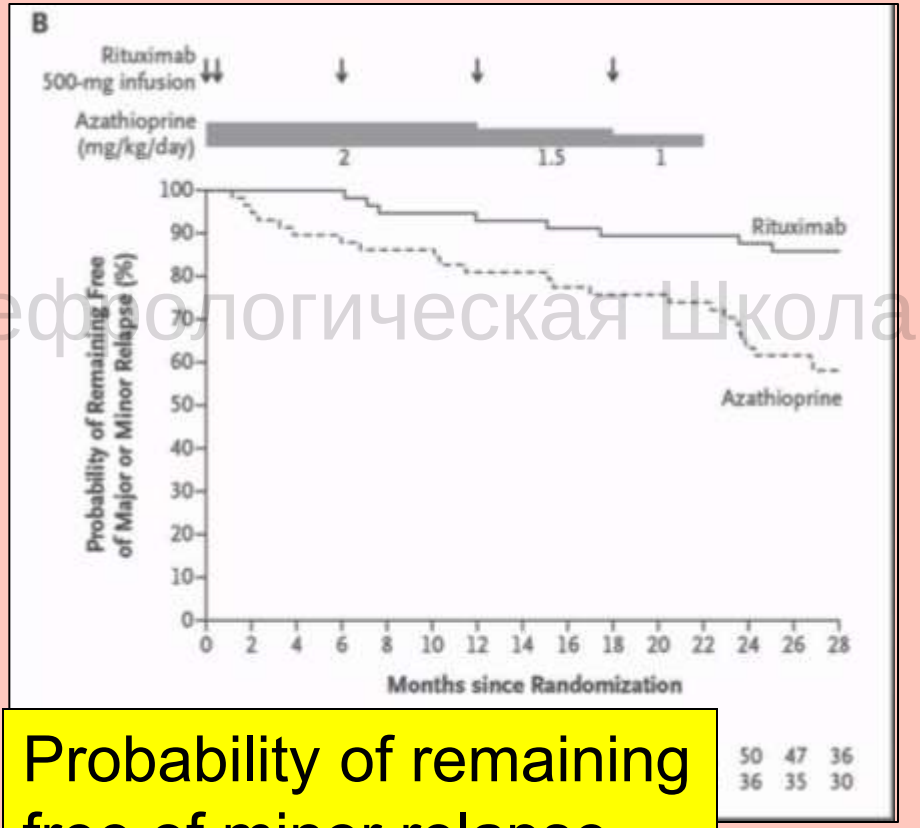
Rituximab (500 mg every 6 mos) is better than AZA as maintenance therapy in AAV

(The MAINRITSAN trial, RCT, 28 mos)



Probability of remaining free of major relapse



Probability of remaining free of minor relapse

Guillevin et al. NEJM 371:1771, 2014

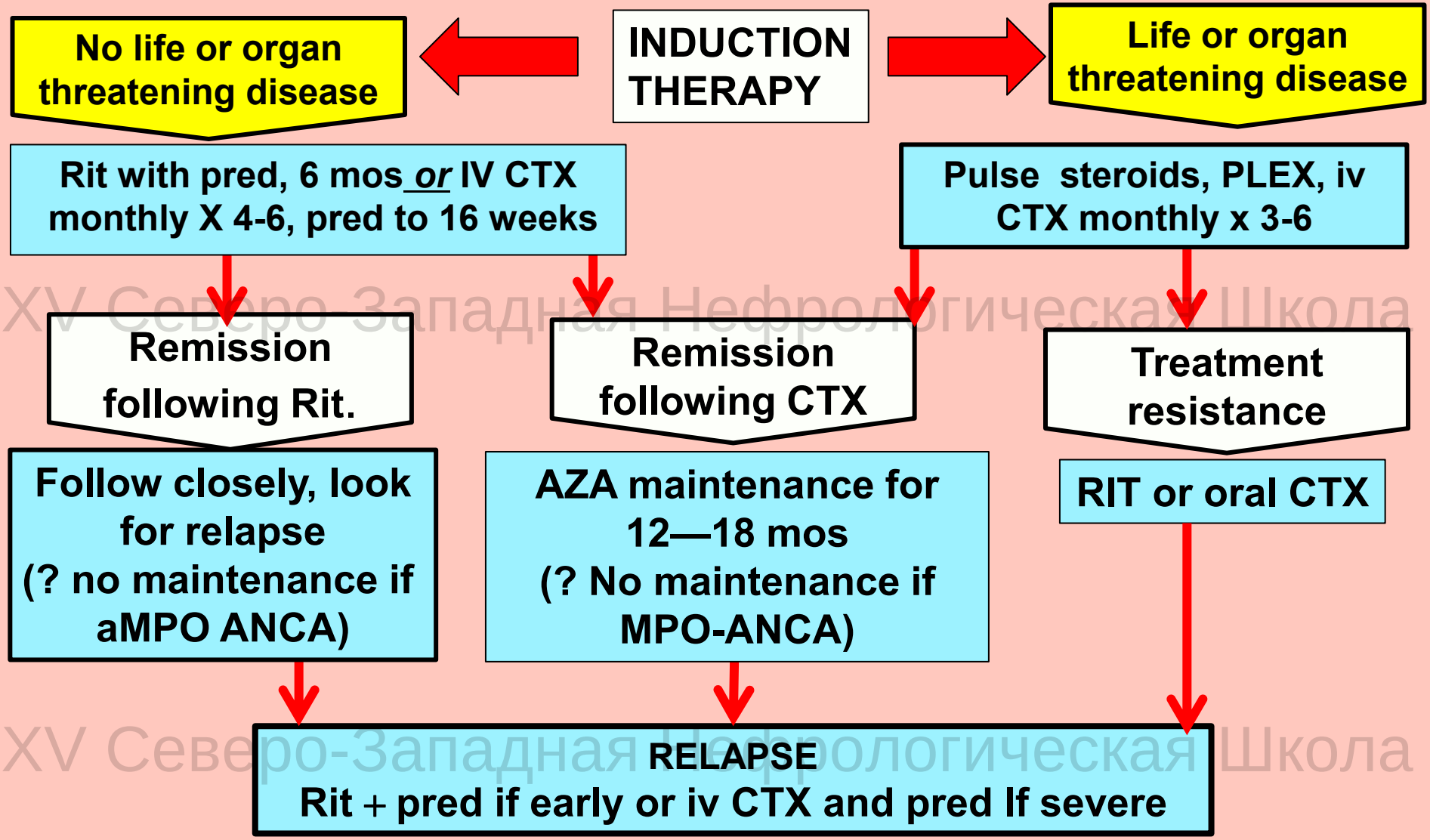
Can repeat RTX be used for maintenance?
Rituximab in chronically relapsing AAV

Group	Initial response	Time to relapse	Relapse rate (2 yrs)
A. RTX induction *Repeated at relapse*	93%	12 mos	73%
B. RTX induction *Repeated every 6 mos*	96%	29 mos	12%
C.Relapsed *Group A switched to B*	95%	35 mos	11%

Kattah, Fervenza et al, Autoimmune Rev 12:854, 2013

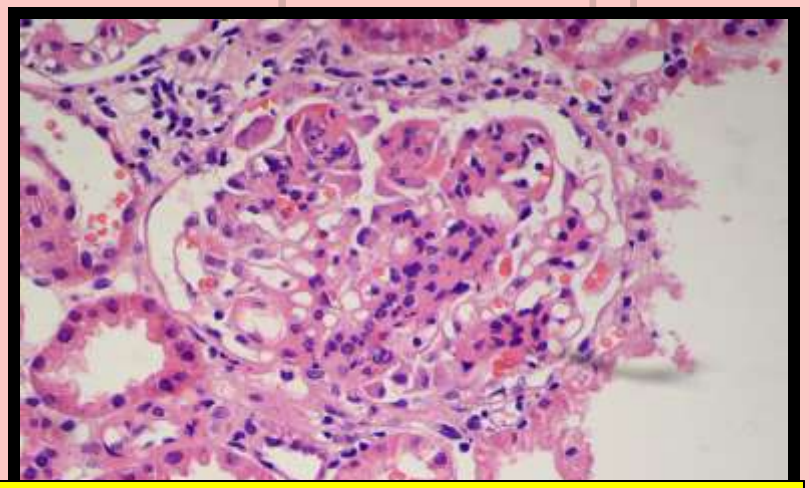
Treatment of AAV (June, 2016)

(Modified from Pendergraft and Falk. JASN 26:771 2015)

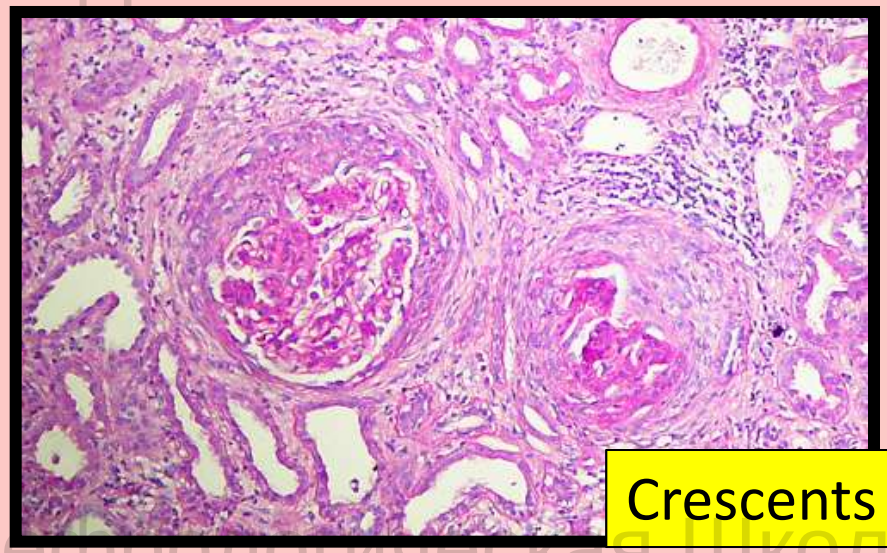


Take home messages - AAV

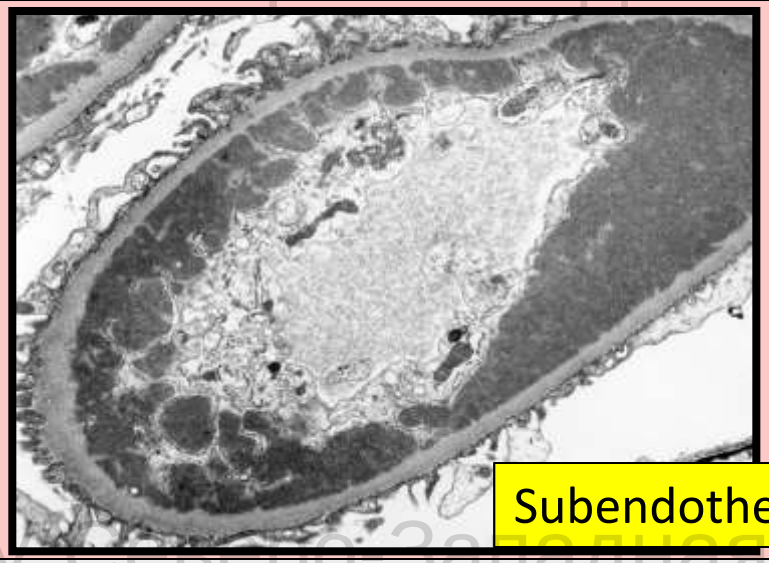
Lupus nephritis, Class III-IV

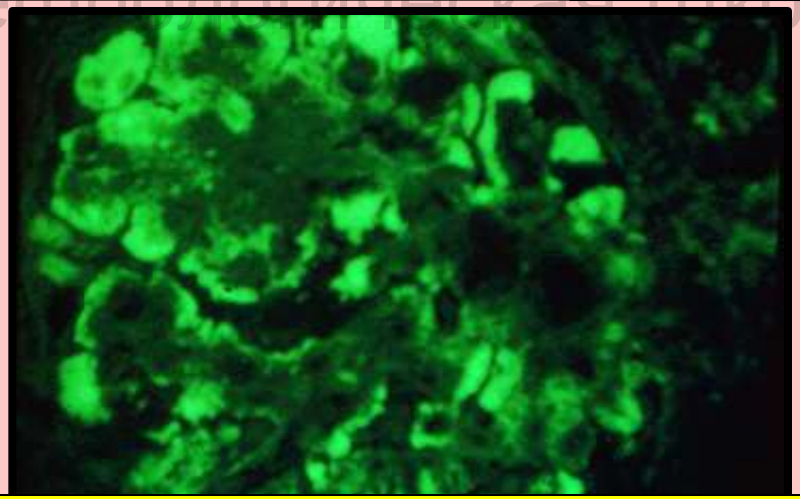


Class III) < 50%; Class IV >50%



Crescents

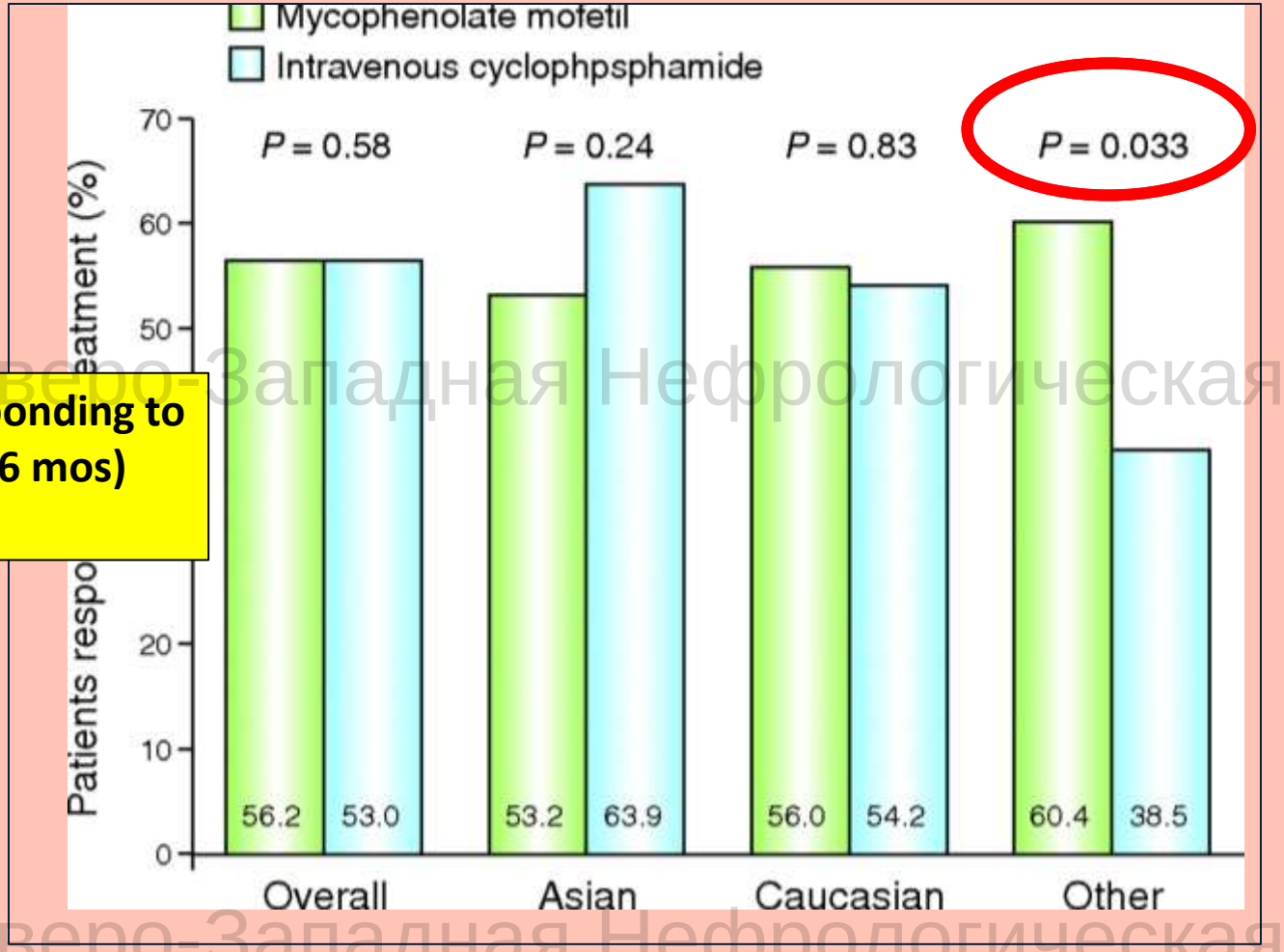




Subendothelial, mesangial deposits of IgG, IgM, IgA, C3

Weening JJ et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* **15**: 241, 2004 (The ISN-RPS classification)

MMF is equivalent to iv CTX for induction and better in the "other" group (mostly blacks, Hispanics)



MMF

CTX

The ALMS study: Appel et al, JASN 20:1103, 2009

What about patients who present with more severe (eGFR < 30) lupus nephritis?

Post-hoc subgroup analysis of patients in the **ALMS trial** with initial **eGFR <30 ml**

Outcome	Induced with MMF	Induced with CTX	P

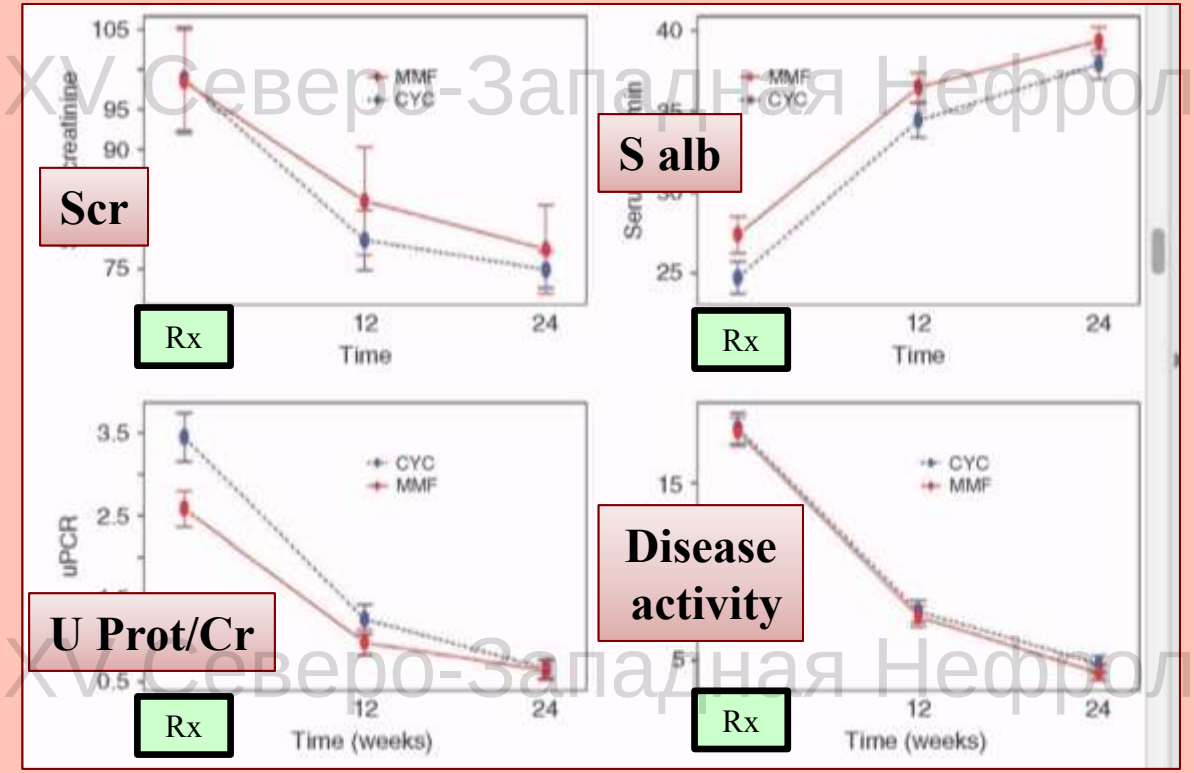
MMF was as effective as CTX and significantly safer In patients with initial GFR <30 ml/min

Walsh et al. Am J Kidney Dis 61:710, 2013

Red = total ALMS cohort

Is it necessary to use the high CTX dose used in ALMS? (24 weeks)

- RCT, 24 weeks, steroids/low dose CTX **("Euro-lupus protocol", 500 mg iv every 2 weeks X6)** vs **steroids/MMF, 1.5-3.0 gms/day**).
- Exclude crescents, Scr >3.0 mg/dl



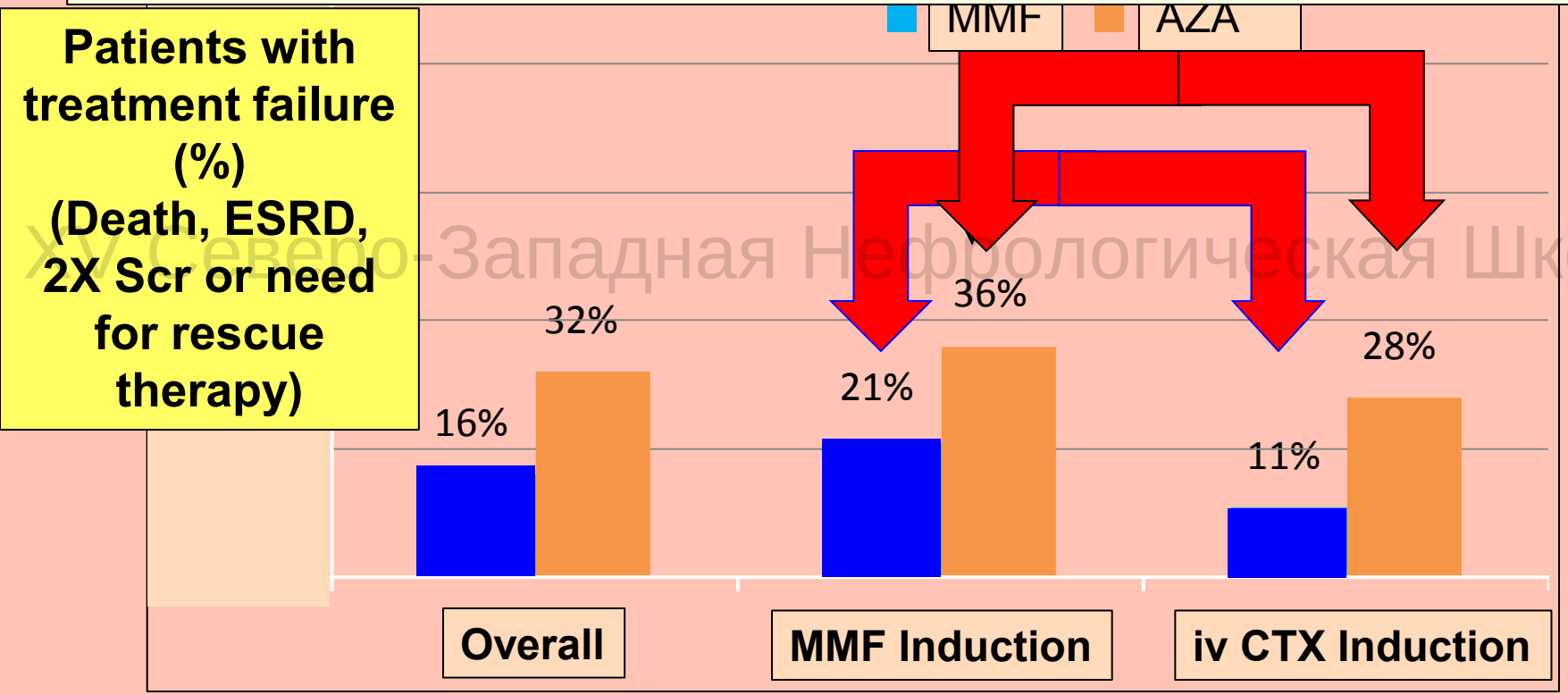
Adverse Events:
MMF = IV CTX except
GI effects higher with MMF

Costs:
MMF 7X CTX

Rathi M, et al. Kidney Int. 89:235, 2016

Maintenance therapy in lupus nephritis
The ALMS study – maintenance phase (3 yrs)

NB: Although not significant, after 3 years of follow up, the patients given CYC induction had fewer treatment failures than those given MMF induction, independent of maintenance therapy



Maintenance therapy for 3 years

Dooley et al New Engl J Med 365:1886, 2011

Induction therapy for Class III-IV LN

(KDIGO CPG for GN (Kidney Int Suppl 2:142, 2012)

Recent data justifies adding CNIs to CTX and MMF as potential alternative induction therapies in lupus nephritis.

*Based on the ALMS trial (Appel et al. JASN 10:1103, 2009

*EULARS guidelines recommend MMF, 3.0 gm/day

Ann. Rheum. Dis. http://dx.doi.org/10.1136/

Steroids/Tac also = Steroids/MMF for induction (in Asian patients)

- **Study design**: RCT, 150 patients, Class III,IV and V, induced with steroids/TAC vs steroids/MMF for 6 mos, then AZA maintenance
- **Results:**
  - Complete remission (6 mos) 59% vs 62% (NS)
  - Proteinuric renal flares (5 years) 24 vs 18% (NS)
  - Decreased GFR by >30%, ESRD or death (5 yrs): 21 vs 22% (NS)

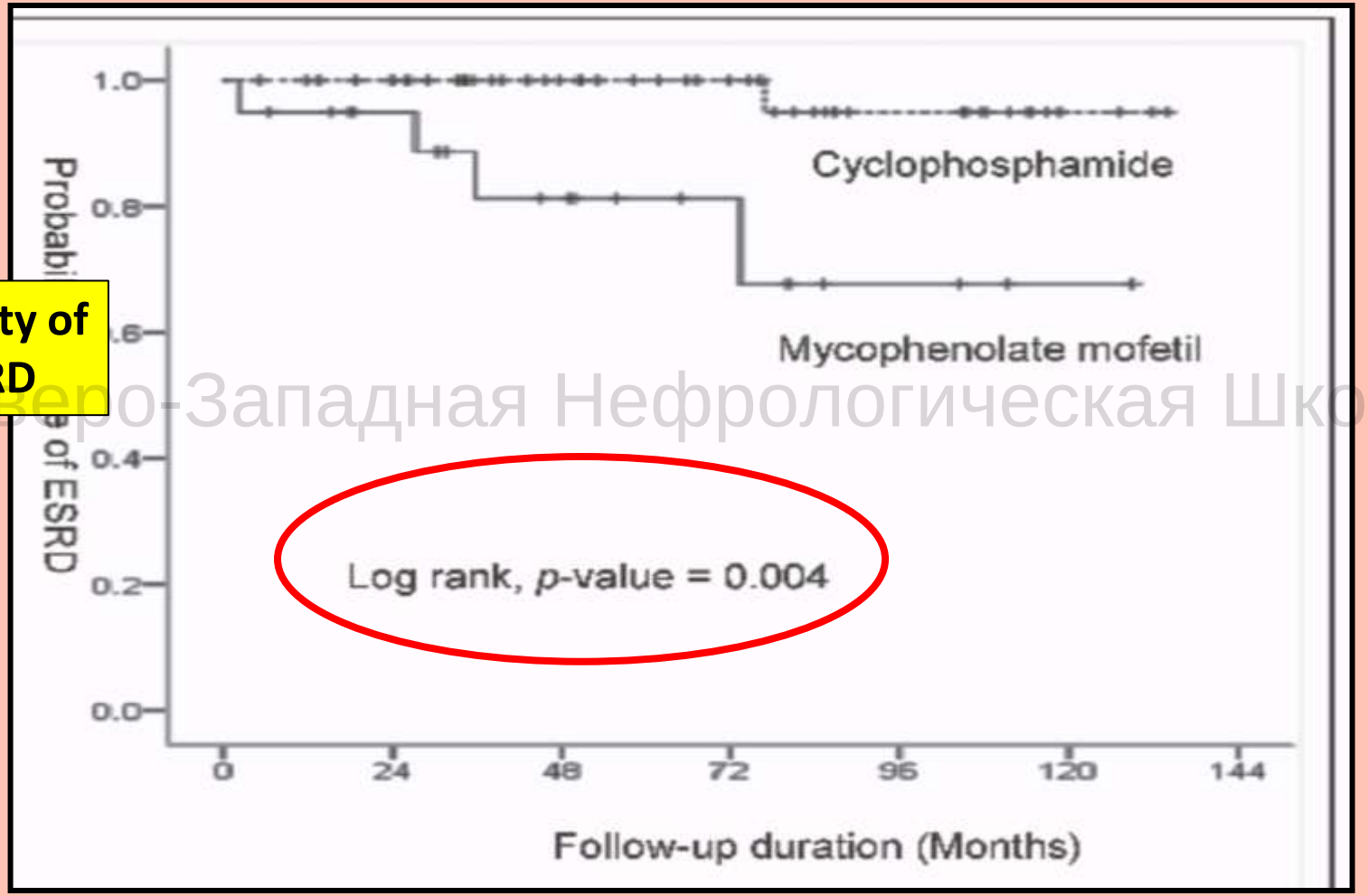
Mok et al. Ann Rheum Dis (Epub 12-7-14)

So is it time to abandon traditional IV CTX protocols for induction in lupus nephritis?

Literature review and personal communications, Rovin et al CJASN 8:147, 2013; Editorial, Bomback AJKD 61:692, 2013.

IV CTX induction increases probability of being free of ESRD at 2-5 years in “severe” lupus nephritis.

Probability of no ESRD



Koo HS et al. Lupus 20:1442, 2011

What do you do if patients do not respond to conventional induction therapy after 6 mos?

Treatment of Refractory LN (About 20-50%)

Lots of options, no data!

- Continue initial induction program for a longer period of time.

- Try "multi-target" therapy (steroids, MMF and CNI (FK)
- Pheresis and/or immunoabsorption
- Iv immunoglobulin

- Immunoablation with or wIthout stem cell transplant

Does adding Rituximab to conventional induction therapy provide additional benefit? THE LUNAR and EXPLORER RCTs

There is a general consensus within the renal community that these two RCTs failed because of defects in trial design, specifically:

1. **Small numbers.**
2. **Use of Rituximab as an add on to standard therapy when patients had failed other drugs first.**
3. **There were more class V patients without much systemic disease in the Lunar trial.**

- **aDNA and C3 levels were also better with Rituximab**

Summary of results adding Rituximab to induction in refractory lupus nephritis

(26 reports, 300 patients, 5 year FU)

LUPUS CLASS	COMPLETE RESPONSE (%)	TOTAL RESPONSE (%)
Class III		
Class IV		
Class V		

Weidenbusch et al. **Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis.** Nephrol Dial Transplant. 28:106, 2013; Reddy et al. **B-cell depletion in SLE: clinical and trial experience with rituximab and ocrelizumab and implications for study design.** Arthritis Res Ther. 2013;15 Suppl 1:S2.

Management of class III-IV lupus nephritis
(maintenance therapy)
(*KDIGO CPG for GN (Kidney Int Suppl 2:142, 2012)*

This guideline will need to be changed to reflect the better results with MMF in the ALMS maintenance phase.

Take home messages: Treatment of lupus nephritis

- **CTX (both high and low dose) = MMF for induction** (Appel et al, ALMS JASN 20:1103, 2009; Rathi et al. Kidney Int 89:235, 2016)
- **But MMF induction results in more relapses and progression later than CTX.** (*Dooley et al New Engl J Med 365:1886, 2011;* Mok et al. Ann Rheum Dis 75:30, 2016)
- **Calcineurin inhibitors may be equivalent to MMF for induction.** (Mok et al. Ann Rheum Dis 75:30, 2016)
- **MMF is superior to AZA for maintenance.** (*Dooley et al New Engl J Med 365:1886, 2011)*
- **Despite two negative RCTs, there is increasing enthusiasm for Rituximab as induction therapy in patients who have failed CTX, MMF and CNIs.** (Rovin et al CJASN 8:147, 2013) Bomback AJKD 61:692, 2013)
- **Rituximab may be effective for induction <u>without oral steroids</u>** (Condon et al. Arth Rheum Dis 72:1260, 2013)

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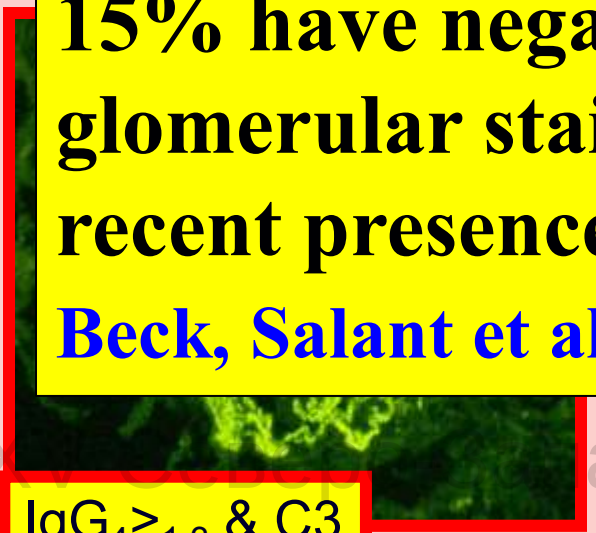
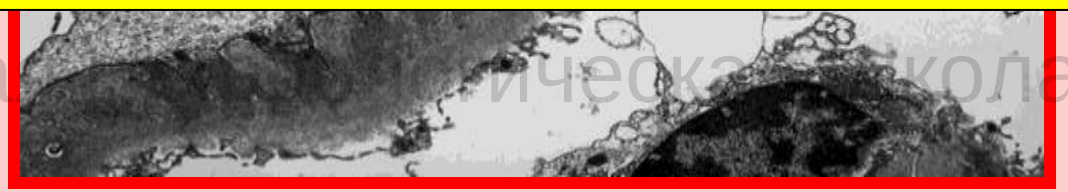
Primary Membranous Nephropathy





The IgG_4 antibody deposits in primary MN were shown in 2009 to represent antibody against the M-type phospholipase A2 receptor (PLA2R) on the podocyte cell membrane. About 75% of patients will be PLA2R-positive and another 15% have negative antibody but positive glomerular staining for PLA2R indicating recent presence of anti-PLA2R.

Beck, Salant et al. New Engl J Med 361:11, 2009

Basics of therapy in primary membranous nephropathy

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Current status of anti-PLA2R antibody (1)
(June, 2016)

Reviewed in Francis, Beck and Salant: Membranous nephropathy: A journey from bench to bedside. Am J Kidney Ds (in press, 2016)

Current status of anti-PLA2R antibody (2)
(June, 2016)

Reviewed in Francis, Beck and Salant: Membranous nephropathy: A journey from bench to bedside. Am J Kidney Ds (Epub 4-13- 2016)

Spontaneous remissions in primary MN

Polanco et al. JASN 21:697, 2010; Hoxha, Stahl et al. NDT 30:1862, 2014

Disease-specific therapy of primary MN

First line

- **Cytotoxic drugs plus steroids**
  - Cyclophosphamide/prednisone
  - Chlorambucil/prednisone (Ponticelli regimen)
- **Calcineurin inhibitors**
  - Cyclosporin/prednisone
  - Tacrolimus/prednisone
- **Rituximab**

Second line

- **MMF**
- **ACTH**
- **IV Ig**
- **Azathioprine**

Treatment of persistent nephrotic syndrome in MN

Who to treat

KDIGO CPG for GN (Kidney Int Suppl 2:142, 2012)

Although anti-PLA2R levels do predict outcomes, we do not know yet if treating patients with increased antibody levels immeadiately (at the time of diagnosis) (vs doing conservative therapy for 6 mos first) would improve outcomes.

What if CTX is declined, contra-indicated or does not work?

Although CNIs are the officially recommended second choice for treating PMN, a recent UK RCT published after the KDIGO guidelines (Lancet 381:744, 2013) showed no difference between steroids/CSA and supportive care in preventing progression.

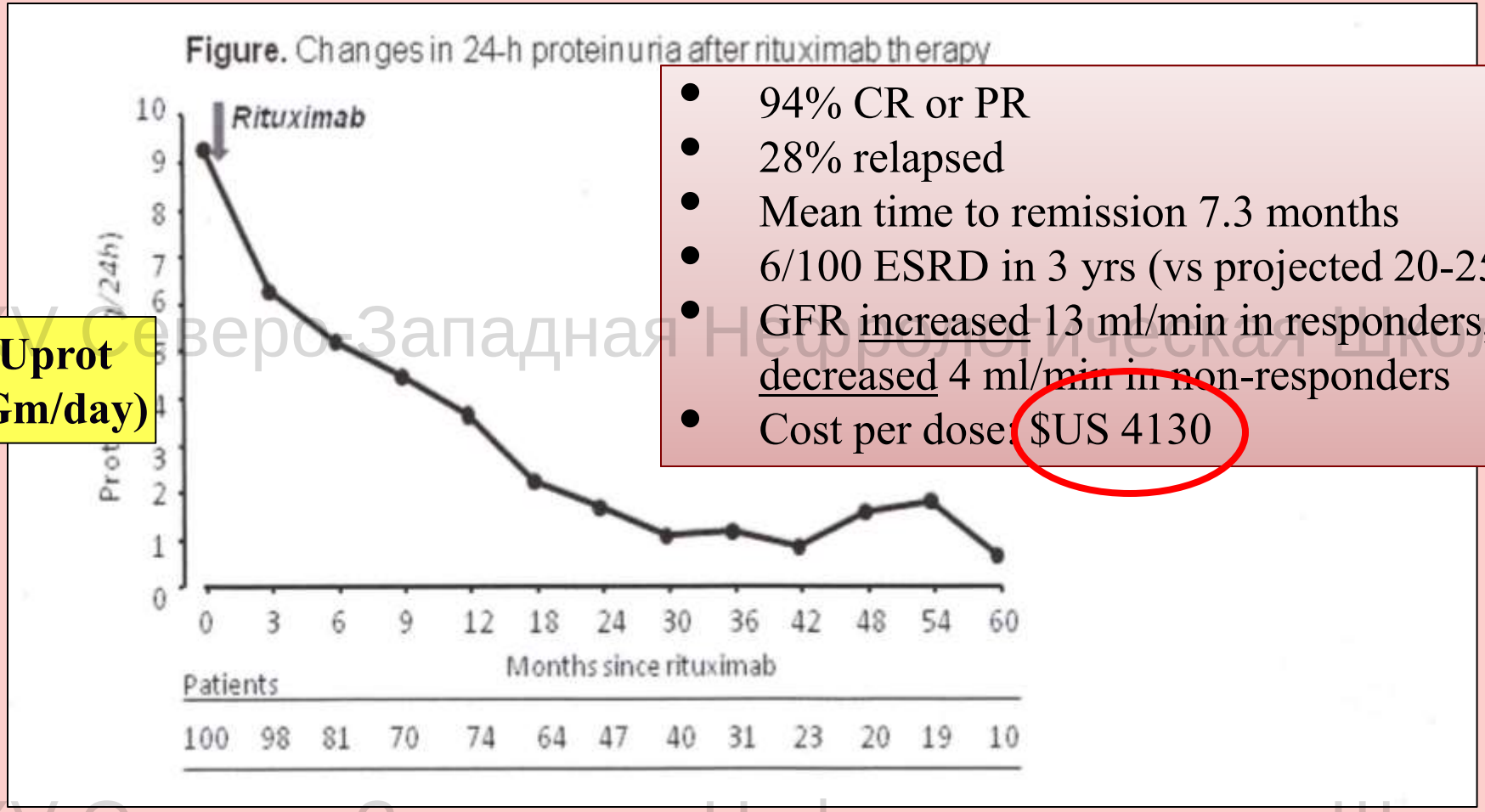
with CSA (or Tacrolimus) increases with duration of therapy (CR 7% at 6 mos but about 40% at 18 mos) and relapse rates also decrease with longer periods of therapy.

- Treat for 1-2 years and taper gradually

Rituximab in primary MN - 5 yr FU

100 pts, cohort study, Up >3.5 gms after 6 mos of ACEI

(Rituximab, 375mg/M^2 X1 repeated only if B cells returned within 6 mos)



Uprot (Gm/day)

- 94% CR or PR
- 28% relapsed
- Mean time to remission 7.3 months
- 6/100 ESRD in 3 yrs (vs projected 20-25)
- GFR increased 13 ml/min in responders, decreased 4 ml/min in non-responders
- Cost per dose: $US 4130

Ruggenenti P et al. JASN 23:1416, 2012

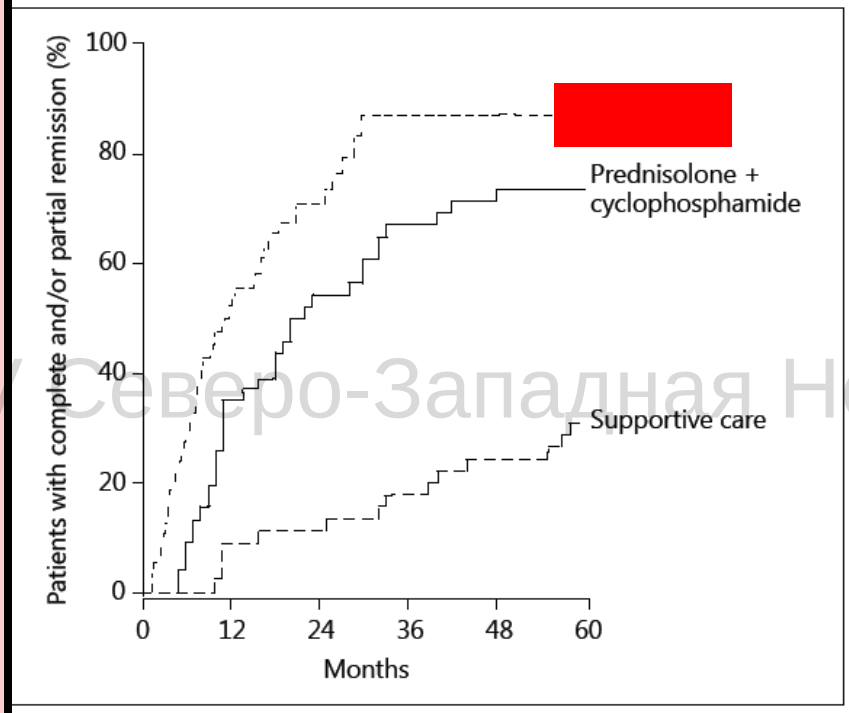
Serious adverse events

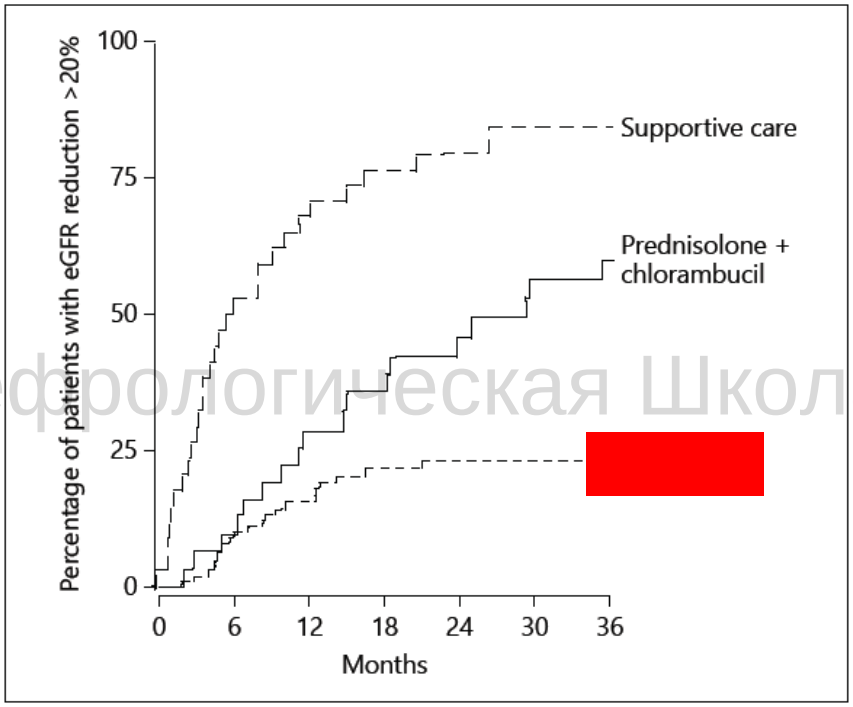
Steroids/CTX vs Rituximab vs conservative therapy in primary membranous nephropathy

Event	Steroids/CTX (n=91)		Conservative (N=130	p
Low WBC	35		2	<.01
Low plts	8		0	<.05
Liver toxicity	8		0	<.05
High blood sugar	11		1	<.01
Infection	33		1	<.01
Hematuria/cystitis	1		0	NS
CVD	20		6	<.05
Cancer	15		3	<.05

From Cravedi et al. Rituximab in primary membranous nephropathy – First line therapy, Why not? Nephron Clinical Practice 128:261, 2014

Effects of Rituximab monotherapy on proteinuria and renal function in primary MN





% patients achieving complete or partial remission in proteinuria

% patients experiencing >20% reduction in GFR

From Cravedi et al. Rituximab in primary membranous nephropathy – First line therapy, Why not? Nephron Clinical Practice 128:261, 2014.

Treatment of primary membranous nephropathy

Summary - 2016

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Thank you!

спасибо

spasibo

Induction therapy of Class V LN

(KDIGO CPG for GN (Kidney Int Suppl 2:142, 2012)

Preserved Renal Function/sub-nephrotic Proteinuria

- **Hydroxychloroquine**
- **Renoprotection (ACEI/ARB)**
- **Immunosuppression**

Nephrotic Proteinuria (>3.5 gms/day or Up/Cr > 3)

- **Steroids plus 6 months of:**
- **Hydroxychloroquine**
- **Renoprotection**

Plus:

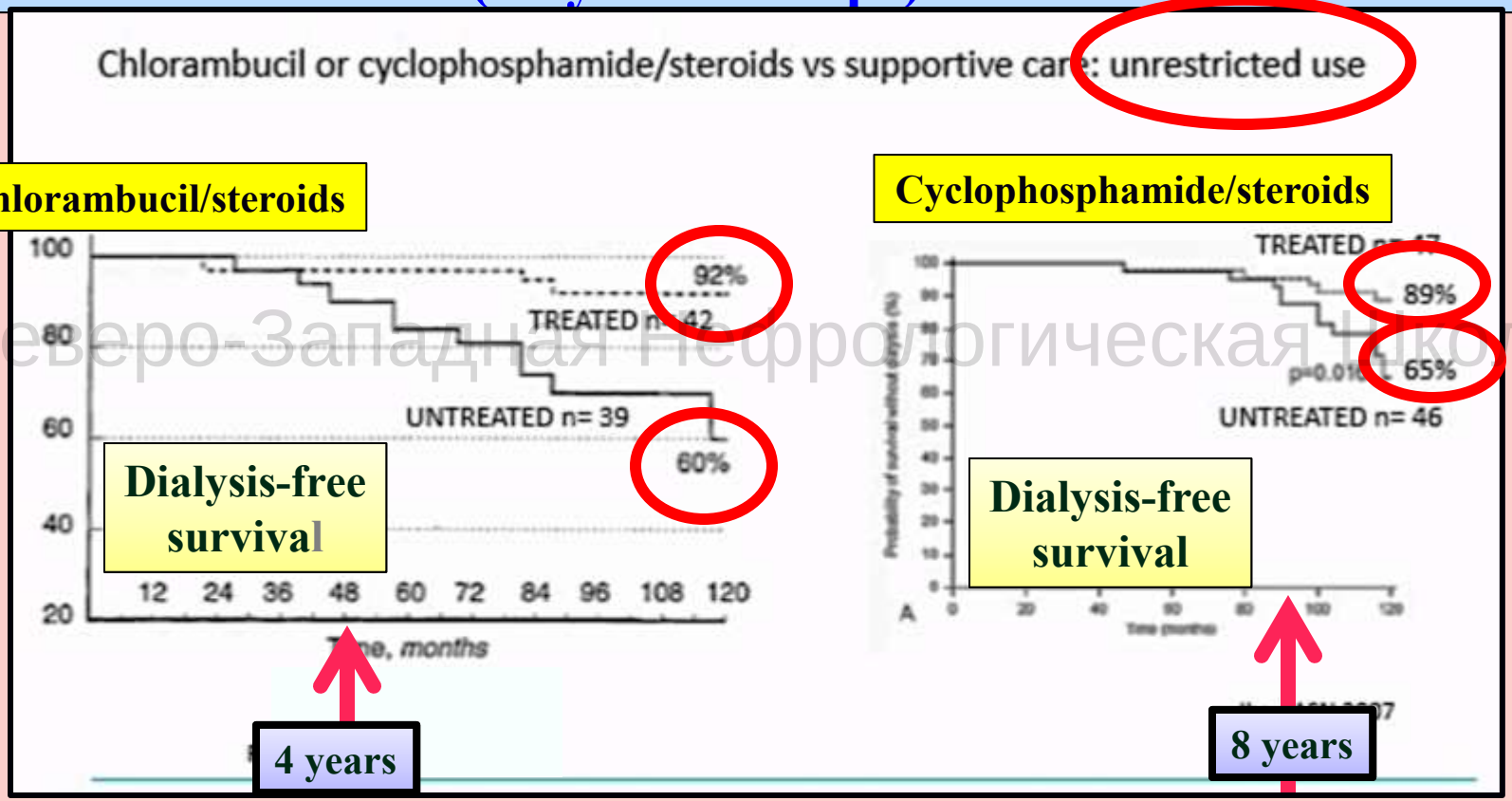
- **MMF (2D) (ACR Recommends)**

There is no published data yet on Rituximab in membranous lupus. However, the Rituxilup study reported a 37% response in lupus membranous at one year (without steroids) vs 7% in ALMS

Condon et al. Arth Rheum Dis 72:1260, 2013

Old news: Alkylating agents for all patients improve renal outcomes in primary MN

(10 yr follow ups)

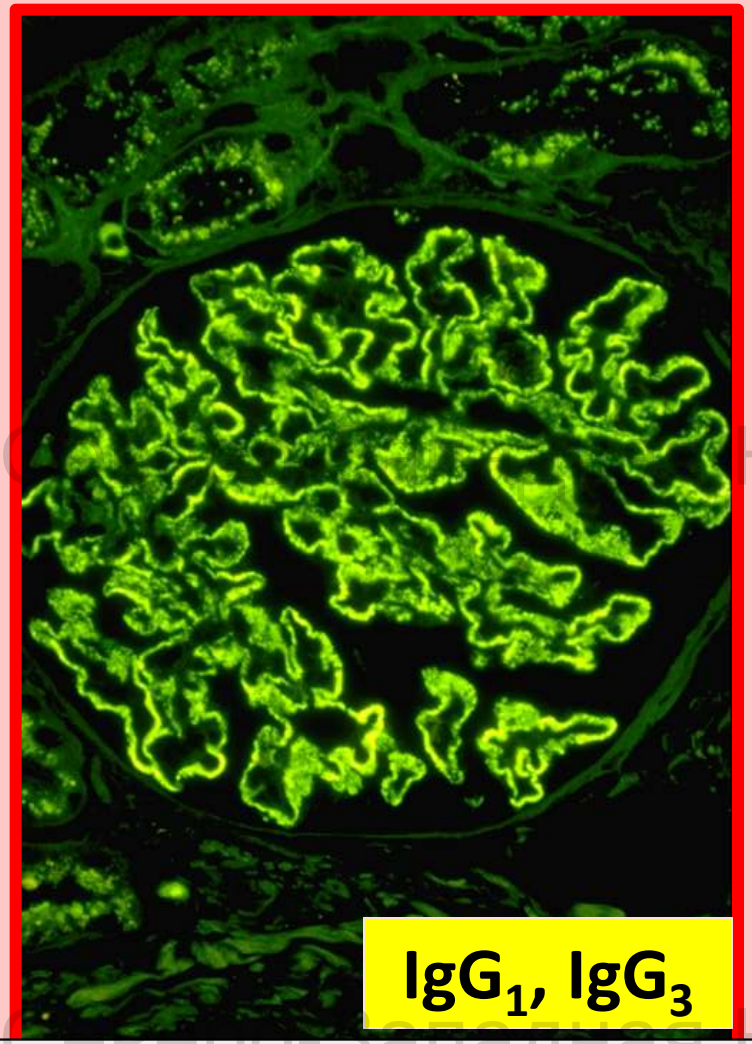


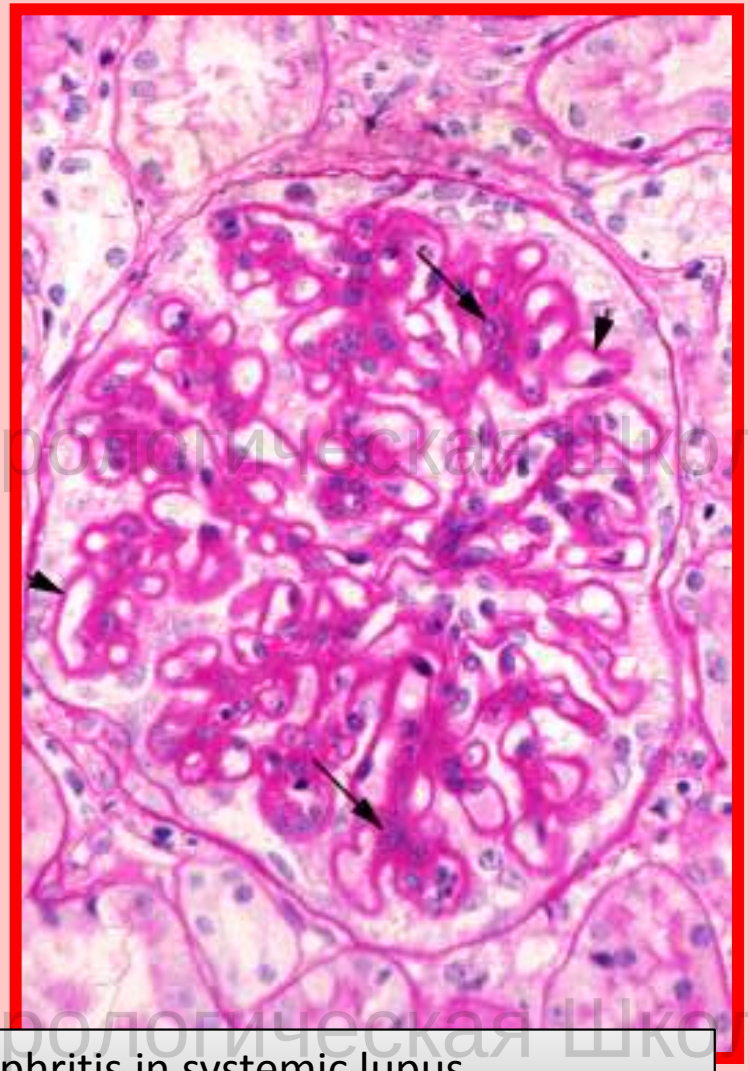
Ponticelli et al, NEJM 310:946, 1984; Kidney Int. 48:1600, 1995

Jha et al. JASN 18:1899, 2007

From Hofstra J: presented at WCN 2015, Capetown, SA

CLASS V LUPUS NEPHRITIS (15%) (MEMBRANOUS)





Weening JJ et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* **15**: 241, 2004 (The ISN-RPS classification)

Summary: Treatment of lupus nephritis: 2016

Treatment goal: Normal (or stabilized baseline) GFR, Uprotein <500 mg/day, inactive (<5 RBCs/hpf) urine sediment)

Although not included in current KDIGO guidelines, there is good evidence that PLEX is also useful in lupus nephritis if there are signs of TMA in the biopsy.

Li et al. Medicine 95:3595, 2016

Summary: Treatment of lupus nephritis: 2016

Treatment goal: Normal (or stabilized baseline) GFR, Uprotein <500 mg/day, inactive (<5 RBCs/hpf) urine sediment)

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Can we treat lupus nephritis <u>without steroids</u>?

The “Rituxilup” regimen - pilot study

(Condon et al. Arth Rheum Dis 72:1260, 2013)

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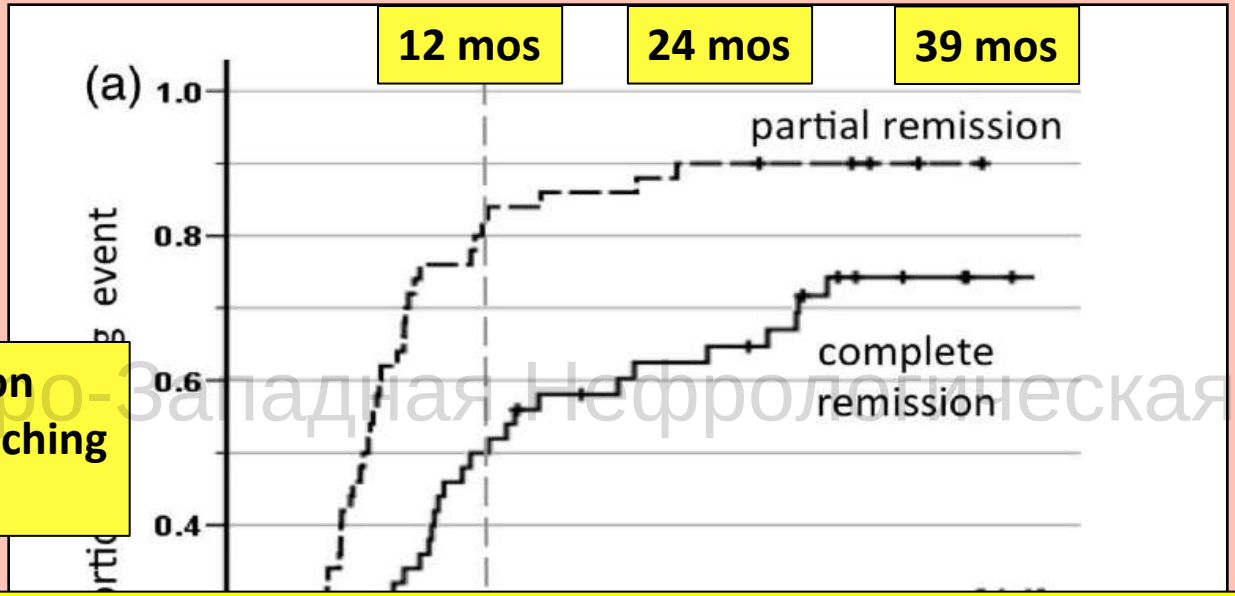
Clinical responses in the Rituxilup study



Proportion of cohort reaching event

A follow-up Rituxilup RCT is in progress comparing MMF/Rituximab with only initial pulse steroids to MMF/steroids

Condon et al. Arth Rheum Dis 72:1260, 2013