The Management of Pauci-Immune Glomerulonephritis

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Unapproved or Off Label Disclosures

This presentation may discuss unapproved or off-label, experimental or investigational use of Cyclophosphamide, MMF, AZA, Rituximab, CSA

A Case of Rapidly Progressive Kidney Failure

A 60 year old white male was found to have acute renal failure with a serum creatinine of 4 mg/dl. Urine dipstick showed large blood and 2+ protein. Previously, the patient had been in good health, took no medications and at his yearly physical 3 months ago his serum creatinine was 0.9 mg/dl. Other than fatigue, decreased appetite and a minor upper respiratory infection a week before hospitalization, there had been no antecedent symptoms. A chest radiograph was unremarkable. Over the next two days the patient became oliguric, SCr increased to 6 mg/dl and he required dialysis.

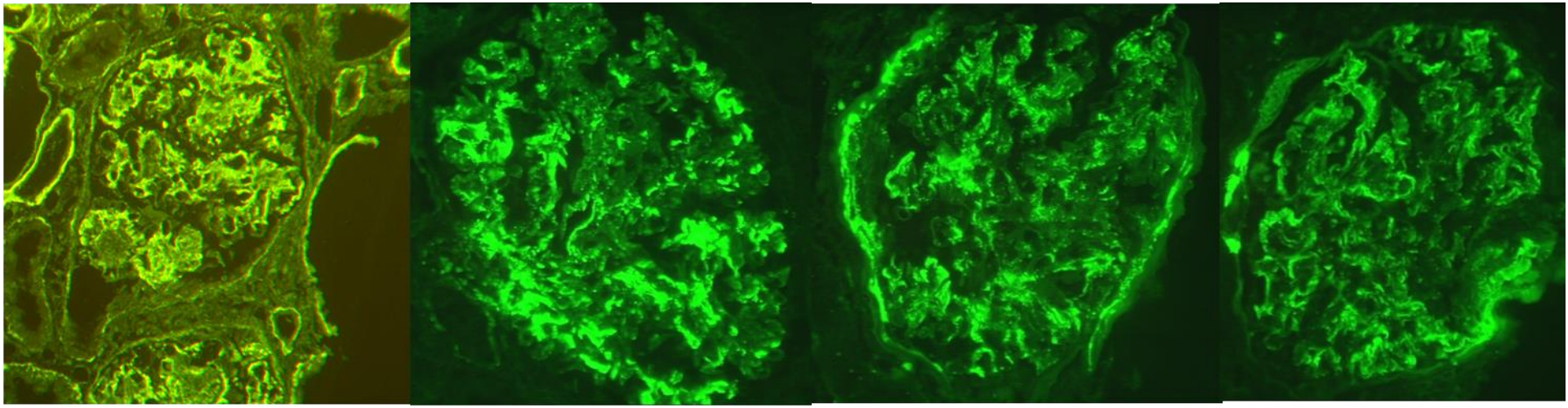
A procedure was performed…

The Patient's Renal Histology

Proliferation, necrosis, crescents and tubulointerstitial damage can be seen in a number of kidney diseases; more histologic and serologic information is needed!

IF Microscopy and Serologic Data

Diagnosis:
Pauci-immune ANCA-associated glomerulonephritis

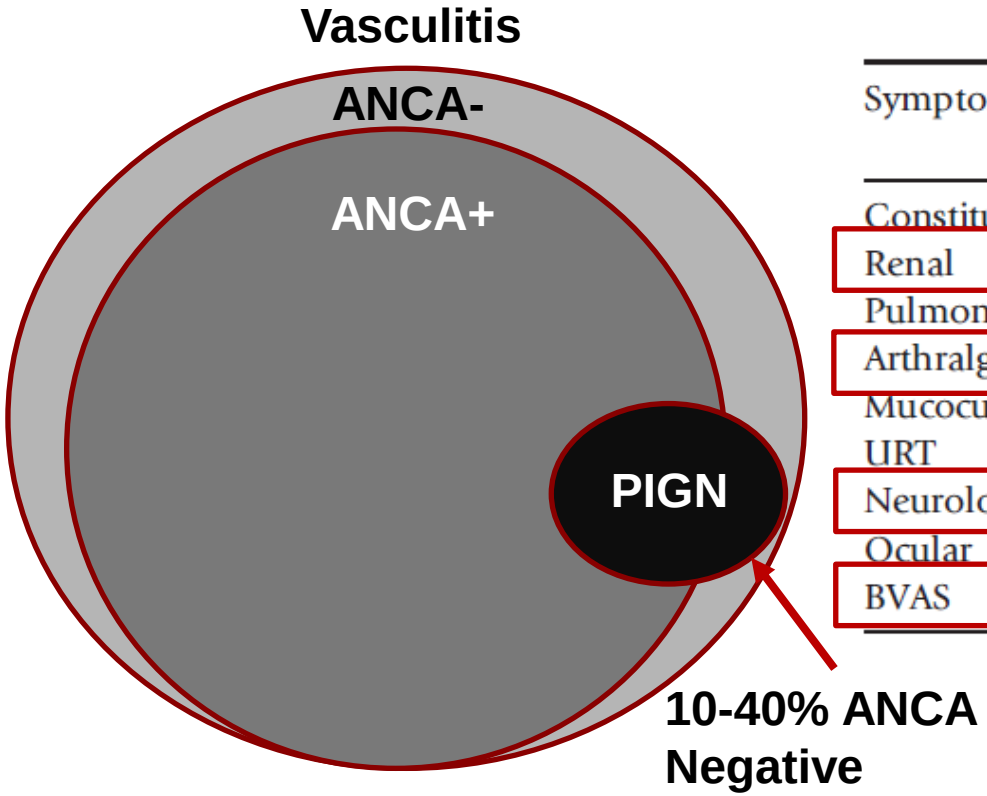


IgG IgM C3 C1q

What is Pauci-Immune Glomerulonephritis?

Pauci-immune GN is a necrotizing, often crescentic GN characterized by minimal immune deposits in the glomeruli; it is frequently accompanied by a rapid deterioration in kidney function

Pauci-immune GN is often associated with anti-neutrophil cytoplasmic antibodies (ANCA) as part of the spectrum of ANCA-Associated Vasculitis (AAV)



Symptoms (%)	ANCA-positive (n = 51)	ANCA-negative (n = 33)	P-value
Constitutional	76.5	78.8	0.41
Renal	74.5	97	0.002
Pulmonary	70.6	60.6	0.18
Arthralgia	39.2	15.2	0.009
Mucocutaneous	19.6	27.3	0.21
URT	25.5	6.1	0.01
Neurological	17.6	0	0.004
Ocular	11.8	3	0.09
BVAS	19.9	15.4	0.001

Sharma et al, Int J Rheum Dis, 2016

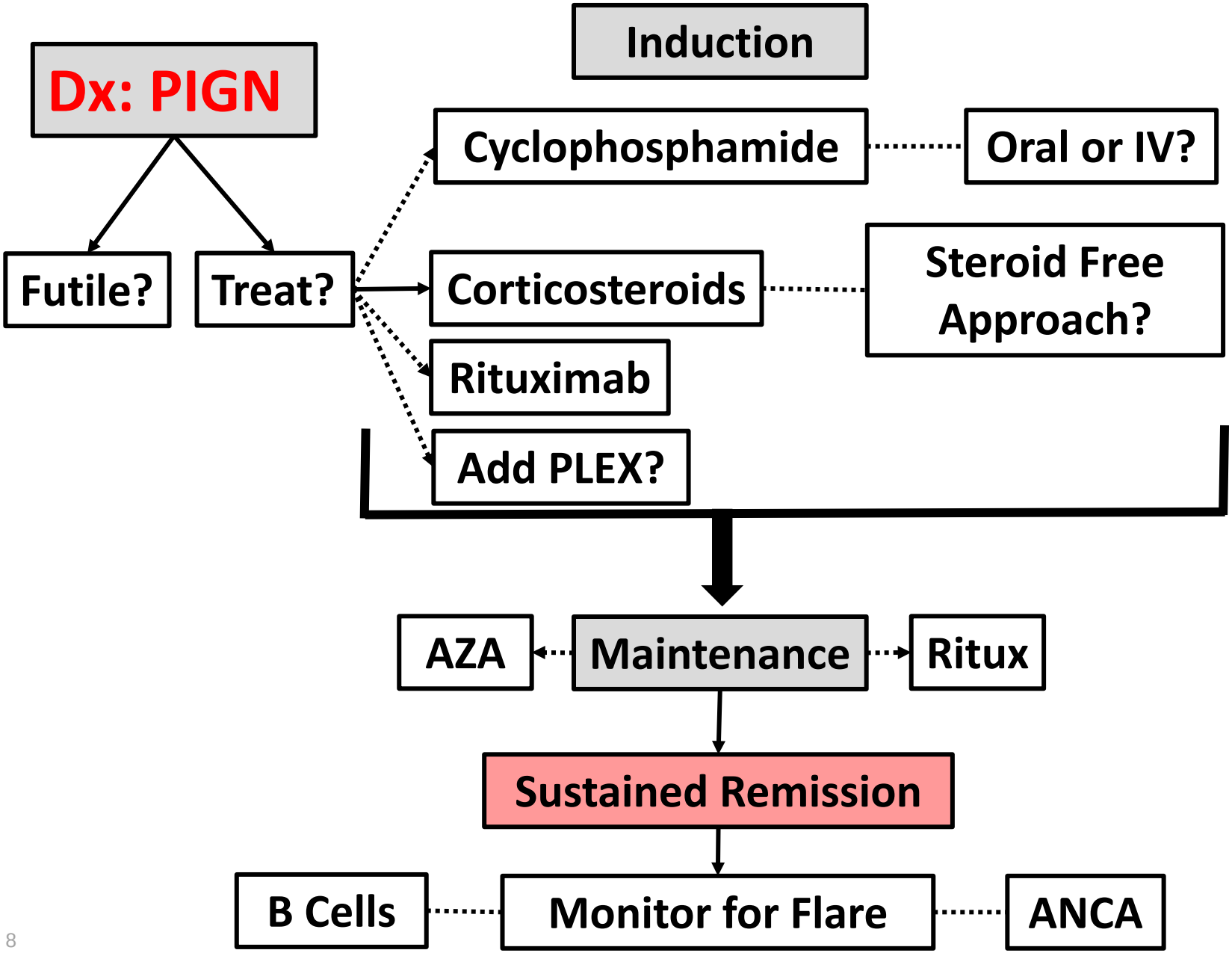
How *Pauci* is Pauci-Immune GN?

	PR3 (n = 55)			MPO (n = 74)		
Glomerular Staining	1+, 2+	>2+	% +	1+, 2+	>2+	%+
IgA	15	2	(30.9%)	22	1	(31.1%)
IgG	20	1	(38.2%)	40	1	(55.4%)
IgM	37	4	(74.5%)	48	6	(73.0%)
C3	39	9	(87.3%)	47	19	(89.2%)
C1q	8	0	(14.5%)	22	0	(29.7%)
C4	2	0	(3.6%)	4	0	(5.4%)

Pauci-immune GN does not mean absence of immune deposits in the glomeruli

Vizjak A, et al. Am J Kidney Dis. 2003;41:539-49

Back to the Patient: Approach to Therapy



When is Treatment for Pauci-Immune GN Futile?

Cohort

- Retrospective AAV population of 155 patients
- Average eGFR: 7 ml/min/1.73 m^2 at presentation; 87% needed RRT
- MPO ANCA 56%; PR3 ANCA 44%
- Renal limited disease: 29%
- Treatment: CYC+steroids-87%; Steroids alone-13%; PLEX added-28%

Independent Variables Associated with Outcomes

ESRD	Death	ESRD + Death
Treatment Response by 4 months	Treatment response by 4 months	Treatment Response by 4 months
HR 0.06; P<0.001	HR 0.09; P<0.001	HR 0.09; P<0.001
	Age <54 years: HR 0.25; P<0.04	CYC use: HR 0.39; P=0.01
	CYC use: HR 0.43; P=0	

Treatment response: Dialysis independent; eGFR >20 ml/min/1.73 m^2 ; no clinical signs of active systemic vasculitis

Variables *not* associated with adverse outcomes were: Histologic Class; ANCA sub-type

Multivariable Model of Response at 4 months

- Induction with CYC: OR=4.4 (compared to steroids alone)
- Baseline eGFR >10 ml/min/1.73 m^2 (compared to eGFR ≤10)
- 1.2 for every unit decrease in biopsy chronicity score

Probability of response is still >14% even with high chronicity on biopsy and eGFR<10 ml/min/1.73 m^2

Lee et al, J Am Soc Nephrol, 2014

Conclusion-Treatment Futility

- **Cyclophosphamide and Corticosteroids should not be withheld from anyone with AAV and Nephritis no matter how poor their initial kidney function or how chronically damaged their kidney biopsy may appear**

- **If there is no treatment response by 4 months the chance of sustained, dialysis-free kidney survival is <5%**

- **This question has not been examined with Rituximab induction**

Lee et al, J Am Soc Nephrol, 2014

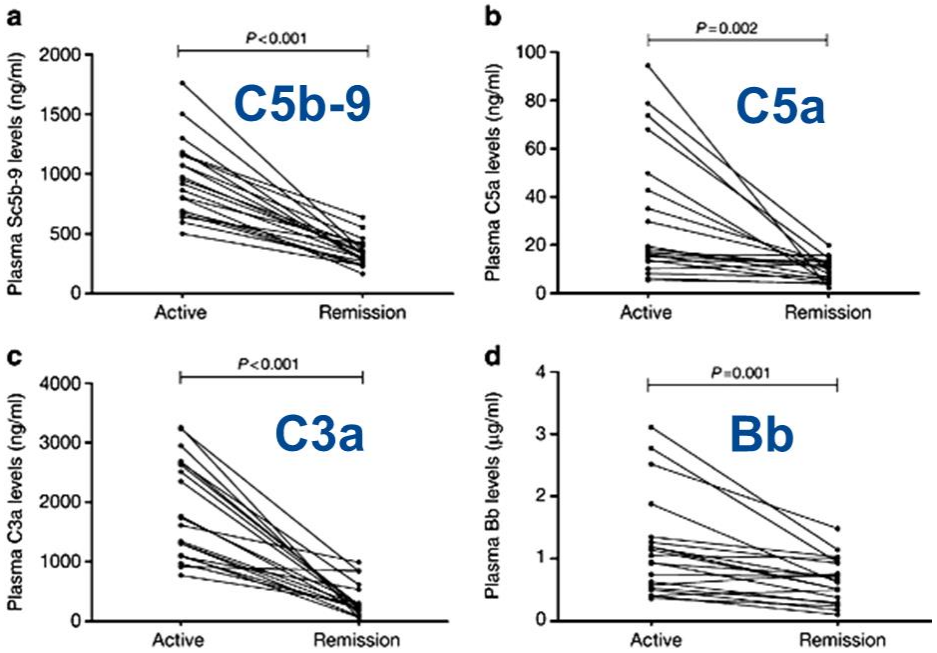
Corticosteroids Are Needed in All Induction Regimens

Recently, this dogma has been challenged by:

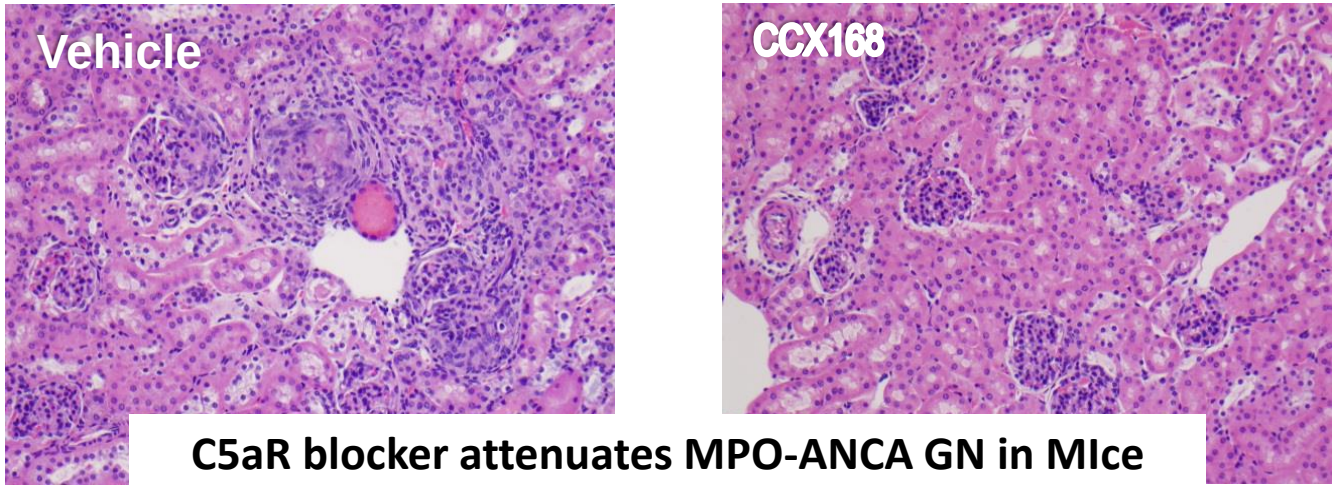
Randomized Trial of C5aR Inhibitor Avacopan in ANCA-Associated Vasculitis

Jayne et al, J Am Soc Nephrol, 2017

Rationale for Complement Inhibition in AAV



Gou SJ, et al, Kidney Int 2012



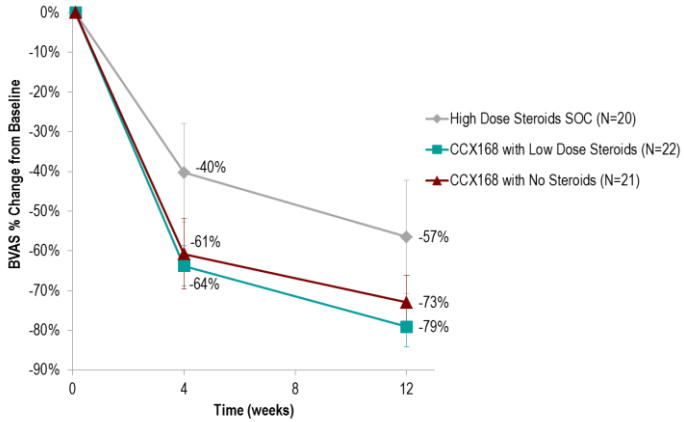
C5aR blocker attenuates MPO-ANCA GN in MIce

Xiao et al, et al, Kidney Int 2012

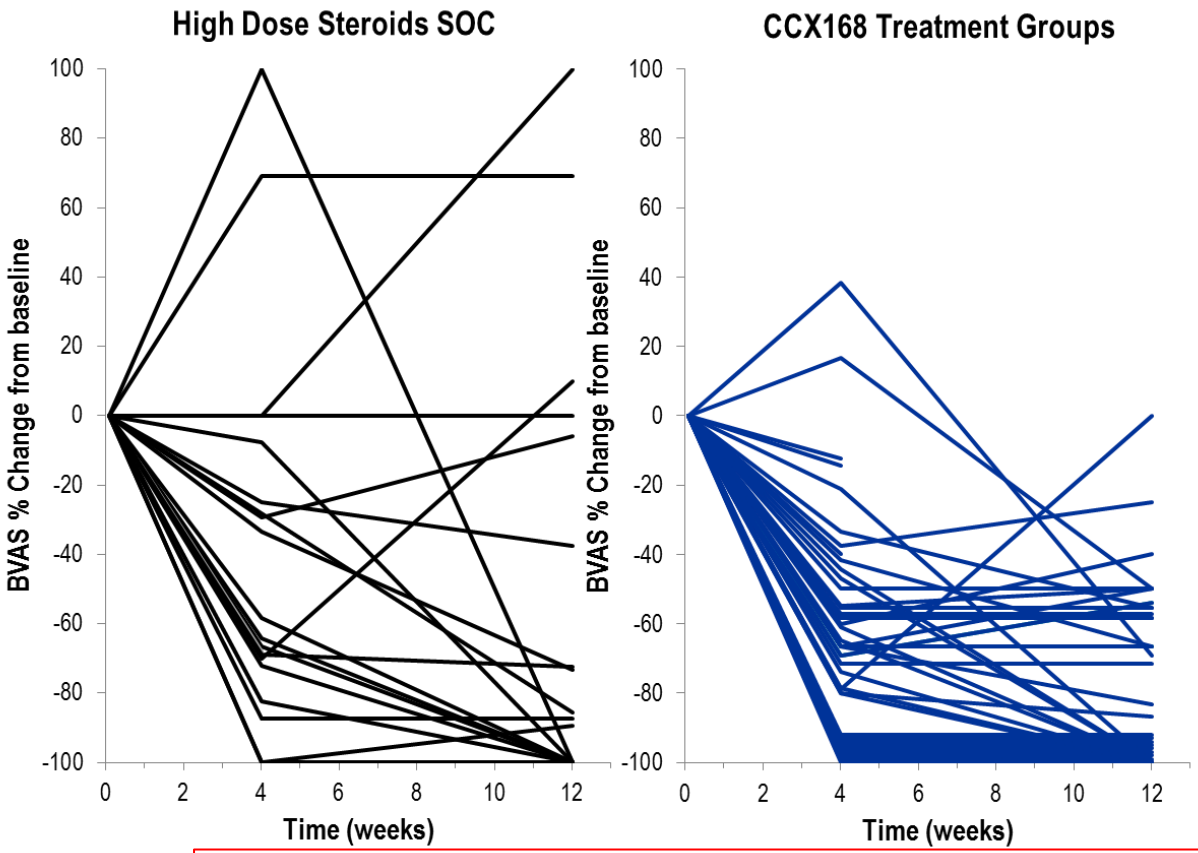
Trial Design and Results

- Randomized, double-blind, placebo-controlled clinical trial in Europe
- Newly-diagnosed or relapsing ANCA-associated vasculitis
- Patients were treated with CYC (81%) or RITUX (19%) for induction immunosuppression
- SOC arm received placebo plus prednisone 60mg/d→10mg/d by week 12
- Experimental arms received C5aR inhibitor plus either low-dose prednisone (beginning at 20mg/d) or no prednisone (steroid free) for 12 weeks
- Primary end-point was the proportion of patients achieving a ≥50% reduction in BVAS by week 12 and no worsening in any organ system

	Number of Patients	%	P-value
High dose steroid SOC BVAS response:	**14 / 20**	**70%**	
CCX168 patients BVAS response:	**36 / 43**	**84%**	**P = 0.002**
CCX168 plus low dose steroid:	19 / 22	86%	P = 0.002
CCX168 plus no steroid:	**17 / 21**	**81%**	**P = 0.01**



Rapidity of Response: *Time is Nephrons*



5% 35% 21% 39%

BVAS=0

Looking Specifically at Renal AAV

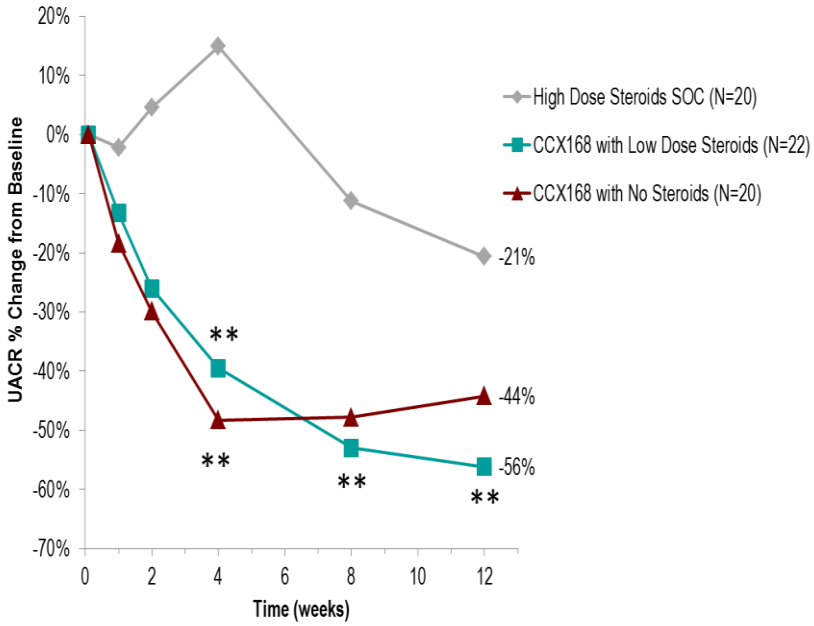
Baseline Characteristics (% of patients)

	SOC	Low Pred	No Pred
Renal Involvement	100%	95%	95%
↑SCr	65%	50%	27%
Hematuria	96%	91%	95%
Proteinuria	78%	91%	73%
Hypertension	13%	23%	9%
eGFR (ml/min)	48	53	55
uALB/Cr	28-5962	24-2459	25-3051

(% Change from Baseline to 12 wks)

	SOC	Low Pred	No Pred
Renal BVAS	-53	-77	-62
Urine RBCs	-92	-83	-85
eGFR	+6	+6	+0.8

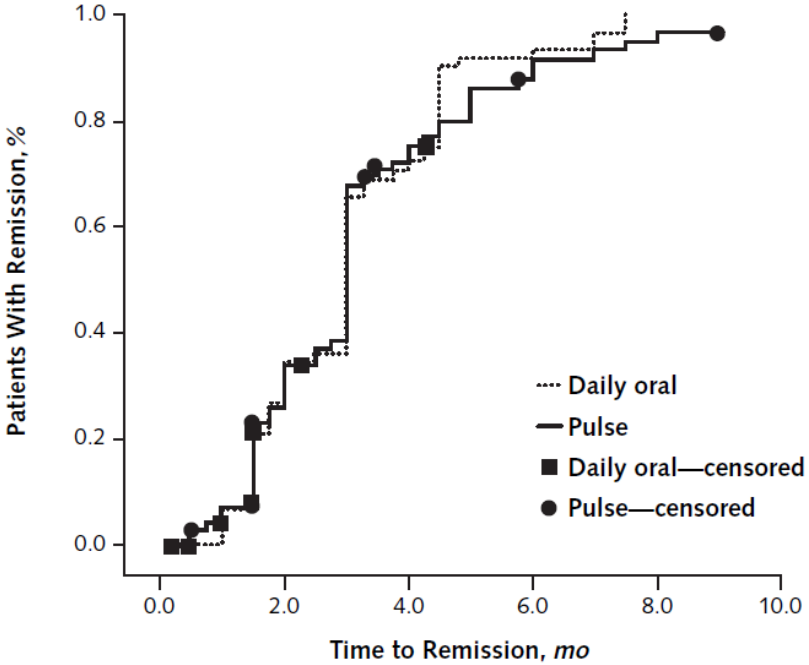
Albuminuria (% Change from Baseline)



A Phase III Trial is Now Underway

Cyclophosphamide for Induction

- **Cyclophosphamide is SOC for induction of remission in AAV, especially severe cases with kidney involvement**
- **Delivery format (ORAL vs INTRAVENOUS) has been prospectively tested**

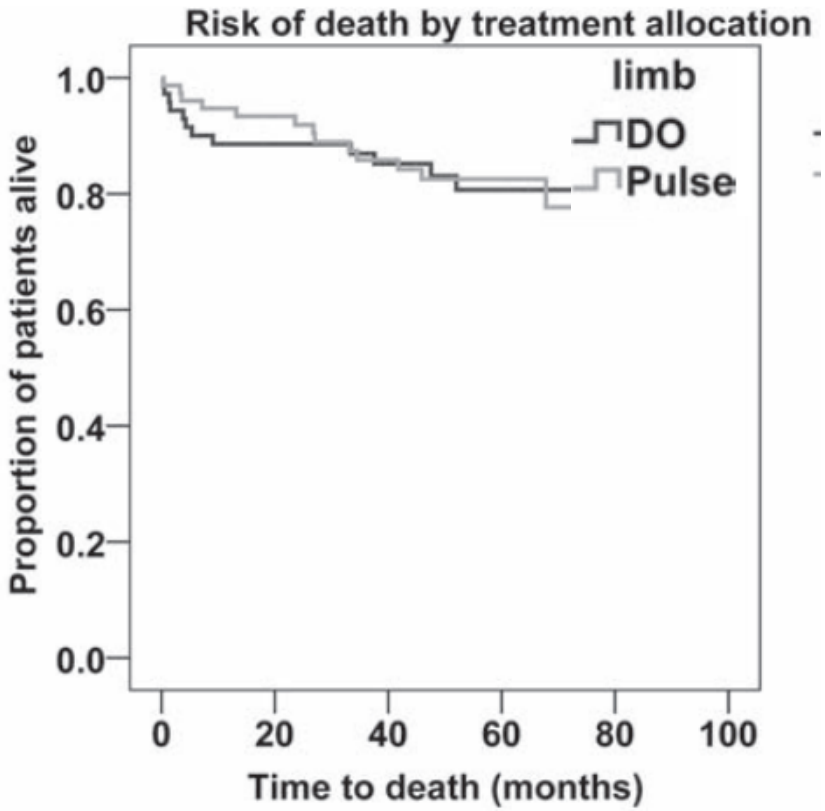


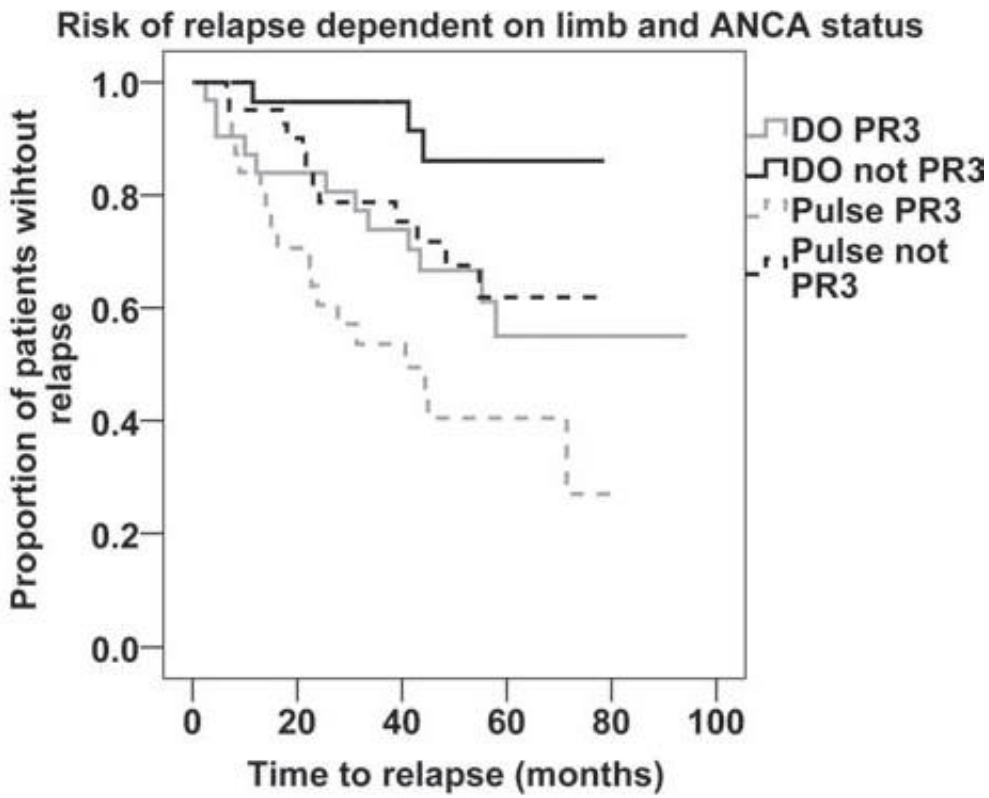
Parameter	Baseline		18 Months	
	Pulse	Daily Oral	Pulse	Daily Oral
Total patients, n	76	73	62	54
Active disease, n	76	73	1	0
Achieved remission, n	0	0	61	54
Died, n(%)	0	0	5 (2)	9 (4)
Relapse after initial remission, n	0	0	13	6
End-stage renal disease, n	0	0	5	1
Median eGFR (IQR), ml/min/1.73m^2	32 (15-52)	29 (18-48)	50(30-70)	48(36-69)
Cumulative cyclophosphamide median dose for patients still in study (IQR), g	0	0	8.58 (6.76-11.9)	18.05 (13.5-27)

- **Oral CYC was given as 2 mg/kg until remission then 1.5 mg/kg for 3 months**
- **Pulse CYC (15 mg/kg) was given at 3 week intervals for 3 months beyond remission**
- **Adverse events were similar between oral and IV CYC; leukopenia was higher in the oral arm**

De Groot et al, Ann Int Med, 2009;

Oral *vs* IV Cyclophosphamide-Long-Term Follow-Up





- **Despite more relapses in the pulse CYC group, there were no differences in last renal function and ESRD (13% IV; 11% Oral)**
- **Relapses were mostly extra-renal; renal relapses were the same between groups**
- **Relapses were higher in PR3 ANCA**
- **No differences in adverse events or overall duration of immunosuppression**

Harper et al, Ann Rheum Dis, 2012

Rituximab for Induction?

On the basis of two trials Rituximab was approved for induction of remission in AAV:

RAVE: Rituximab *vs* Oral Cyclophosphamide

Stone, J. H. *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N. Engl. J. Med.* 363, 221–232 (2010).

RITUXVAS: Rituximab + IV Cyclophosphamide *vs* IV CYC

Jones, R. B. *et al.* Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *New England Journal of Medicine* 363, 211–220 (2010).

Cyclophosphamide has a long track record of success in AAV and PIGN. To replace cyclophosphamide rituximab should provide one or more of the following benefits:

- **Better efficacy in remission induction**
- **Better safety/fewer adverse events**
- **Better long-term preservation of kidney function**
- **Better cost-effectiveness**

RAVE EFFICACY RITUXIVAS

Prednisone + CYC 2mg/kg/d until remission; maintenance AZA 2 mg/kg/d

Prednisone + Ritux 375 mg/m^2 for four doses; no maintenance immunosuppression

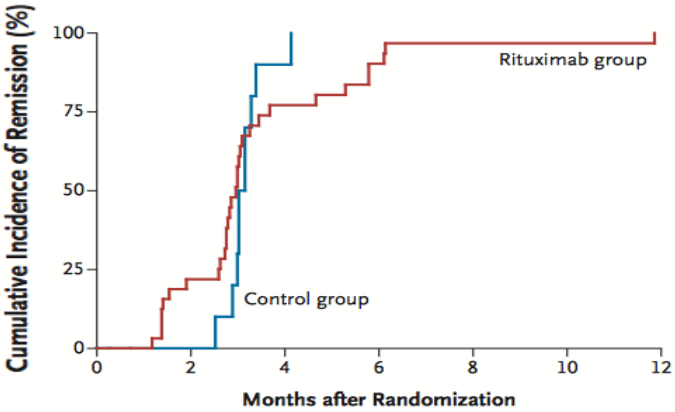
Mean Creatinine Clearance 54-65 ml/min; SCr could not be >4mg/dl

Methylprednisolone→Prednisone + CYC 15 mg/kg IV q2wks X3 then q3wks until stable remission; maintenance AZA 2 mg/kg/d

Methylprednisolone→prednisone + Ritux 375 mg/m^2 for four doses + CYC 15mg/kg IV with the first and third rituximab infusions; no maintenance immunosuppression

Median eGFR ≤20 ml/min/1.73 m^2; dialysis needed in 24% of the rituximab patients

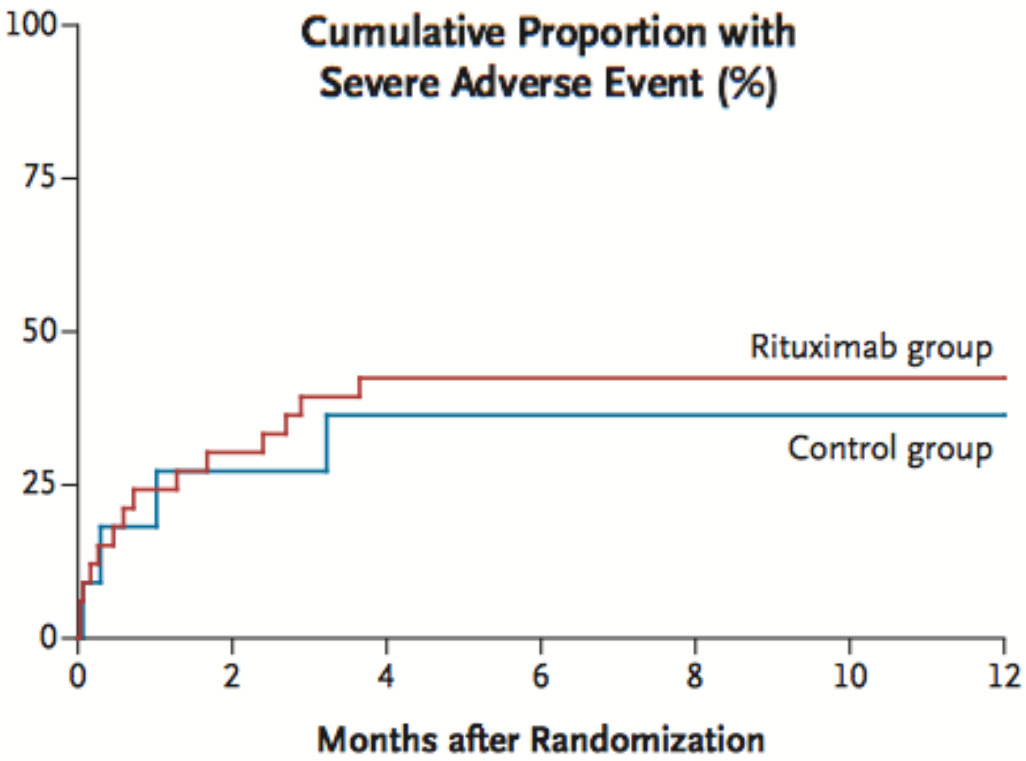
Complete Response 6 Months	RITUX (%)	CYC (%)
On no prednisone	64	53
On <10mg/d prednisone	71	62
Relapsing Disease	67	42



No time course of response was provided for RAVE; for RITUXIVAS the Ritux arm was slower to remit

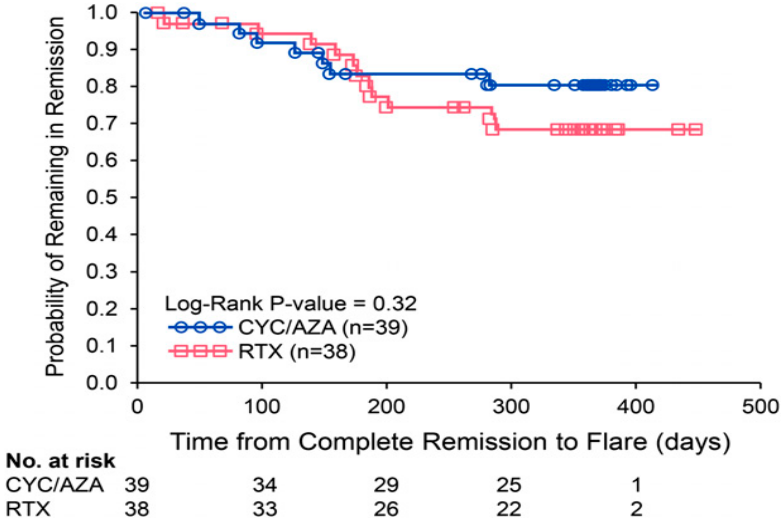
RAVE SAFETY RITUXIVAS

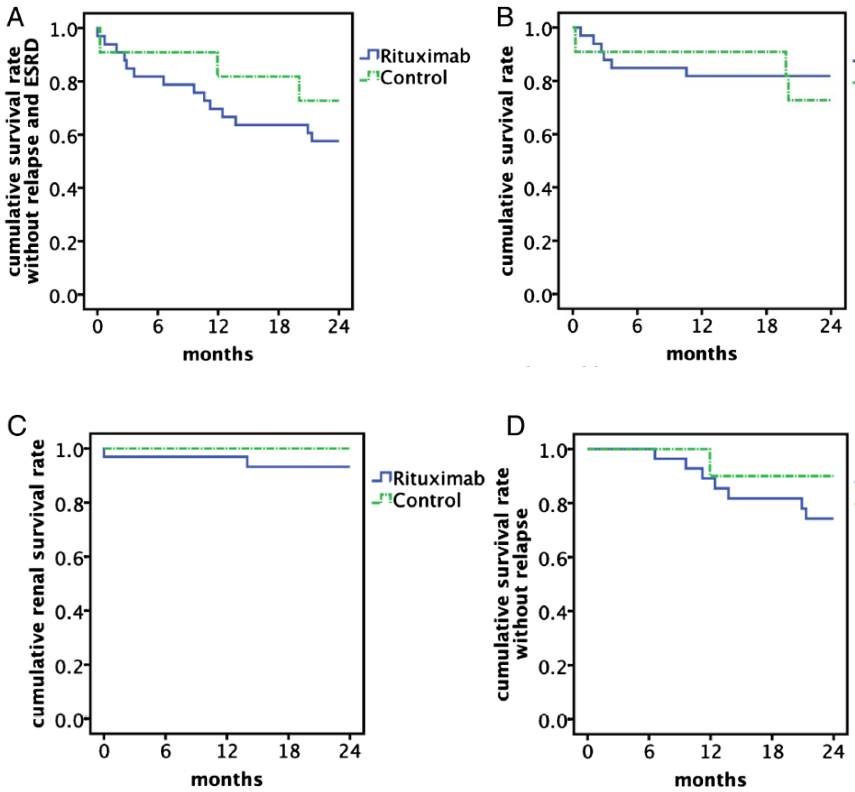
No difference in adverse events between groups; leukopenia was more frequent in the CYC arm



RAVE Long-Term Efficacy RITUXIVAS

This is only the RAVE patients who had Renal Involvement





% in Complete Remission at 6, 12 and 18 Months

CR	PR3		MPO		New Dx		Relapse	
	R	C	R	C	R	C	R	C
6	67	61	52	65	50	69	72	53
12	40	46	52	48	42	59	48	26
18	37	46	52	39	42	53	40	26

None of the differences were significant for either the RAVE or RITUXIVAS long-term data

Geetha, J Am Soc Nephrol, 2015; Jones et al, Ann Rheum Dis, 2015

Do These Studies (Unequivocally) Support Rituximab Over Cyclophosphamide in AAV/PIGN?

No, not yet…

- **There were no differences in outcomes (long or short-term) or adverse events**
- **The RAVE trial did not include patients with severe PIGN**
- **The RITUXVAS trial did include patients with severe PIGN, but these patients were treated with CYC + Rituximab**
- **There are no prospective, randomized trials comparing CYC to Rituximab for severe AAV/PIGN to date, but PEXIVAS may provide answers soon**

Cancer and Choice of Induction Therapy

Patients with AAV have a 1.89-fold increased risk of cancer compared to general population

Treatment†	Patients (n)	SIR* (95% CI)‡	SIR p Value‡	Cyclophosphamide cumulative dose (g), mean (SD)§	Follow-up (years), mean (SD)¶
Only cyclophosphamide	119	3.10 (2.06 to 4.48)	<0.001	7.26 (4.94)	4.92 (3.10)
Only rituximab	41	0.67 (0.08 to 2.43)	0.86	0.00	6.34 (3.56)

Cumulative dose (g)	Patients (n)	N observed malignancies		SIR (95% CI)†	SIR p Value†	RR (95% CI)†	RR p Value†
Cyclophosphamide							
0	89	8	Dose ↑ SIR/RR ↑	1.37 (0.59 to 2.70)	0.47	1 (reference)	
0.1–20	207	31		1.91 (1.30 to 2.71)	0.001	1.39 (0.63 to 3.50)	0.52
20–108	16	5		5.06 (1.64 to 11.82)	0.007	3.69 (0.95 to 12.78)	0.06
Rituximab							
0	167	34	Dose ↑ SIR/RR ↓	2.86 (1.98 to 3.99)	<0.001	1 (reference)	
0.1–6	70	7		1.41 (0.57 to 2.90)	0.47	0.49 (0.18 to 1.13)	0.11
6–18	83	3		0.45 (0.09 to 1.32)	0.10	0.16 (0.03 to 0.50)	<0.001

SIR: Adjusted ratio of observed to expected malignancies

- **These were non-melanoma skin cancers; no significant differences for other malignancies**
- **The striking finding is that rituximab may REDUCE the incidence of malignancies in AAV**
- **Consider rituximab as first choice in previously-treated, flaring patients**

Van Daalen et al, Ann Rheum Dis, 2017

Should PLEX be Added to the Induction Regimen?

- MEPEX-open-label RCT of treatment-naïve European patients with renal AAV who required dialysis or had a SCr >500 µmol/L (5.8 mg/dL)
- Patients were randomized to methylprednisolone 1gm/d X3 or 7 courses of PLEX
- All patients were then given oral prednisolone tapered over 6 months (1mg/kg/d-initial dosing), cyclophosphamide 2.5 mg/kg/d for 3 months, and AZA 2mg/kg for maintenance
- In multivariate analysis renal recovery was associated with PLEX (0.04) but not age, diagnosis (GPA/MPA) or ANCA subtype

Outcome	IV MP n=67	PLEX n=70	P
Renal Recovery 3 months	49%	69%	0.02
Free from Dialysis at 12 months	43%	59%	0.008
Survival at 3 months	84%	84%	NS
Survival at 12 months	76%	73%	NS
Survival Long-Term (median 4 yrs)	49%	49%	0.75
ESRD Long-Term (median 4 yrs)	49%	33%	0.08

- PLEX did not confer a survival advantage long-term
- Infections were major cause of death, more in PLEX group, but not significant
- Many remaining questions: Methyl Pred + PLEX, ritux + PLEX, more PLEX, less severe AAV
- Some answers from PEXIVAS trial after completion

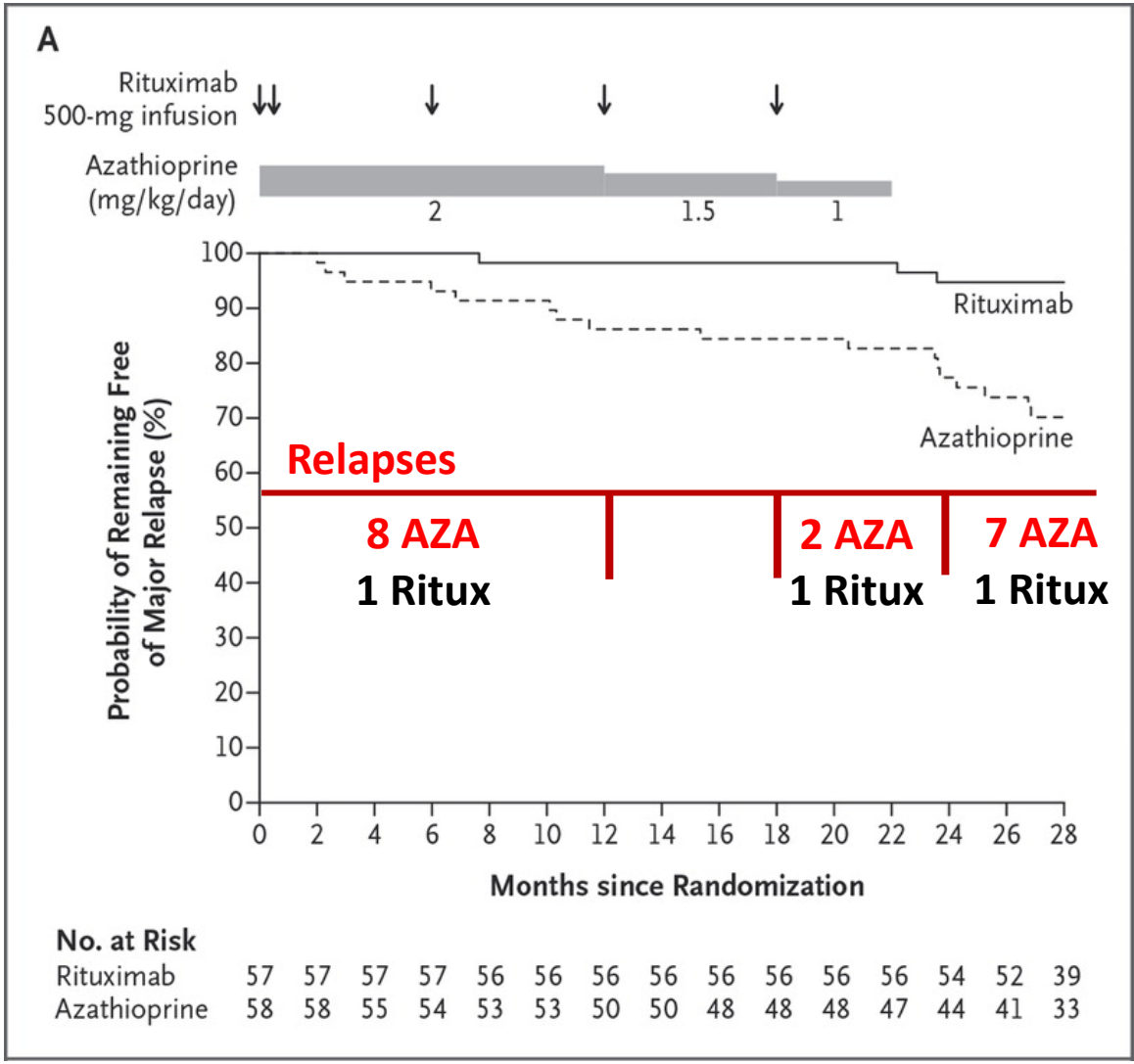
Jayne et al, J Am Soc Nephrol, 2007; Walsh et al, Kidney Int, 2013

Maintenance Immunosuppression for PIGN

- AAV and PIGN are relapsing diseases and it is necessary to keep patients on some form of immunosuppression after induction
- Current SOC for maintenance is AZA; this replaces maintenance with cyclophosphamide and MMF
- The RAVE and RITUXVAS trials challenged this paradigm; in the rituximab arms of both trials no maintenance immunosuppression was given after the initial rituximab administration and steroids were tapered off or down to low levels
- In long-term follow-up of 1.5-2 years the patients in the rituximab arms did as well as the patients in the CYC arms who received AZA for maintenance with respect to survival and relapses
- It was conceivable that rituximab may be good for long-term maintenance in AAV

AZA *vs* Rituximab for Maintenance of AAV

- Remission was induced with prednisone, CYC and some patients received pulse MP
- CYC was 0.6 gm/m^2 on days 0, 14, 28 and then 0.7 g/m^2 every three weeks until remission
- 17 major relapses occurred in AZA group; 3 in the rituximab group
- 8 of the major AZA relapses involved the kidney; none of the rituximab relapses were renal



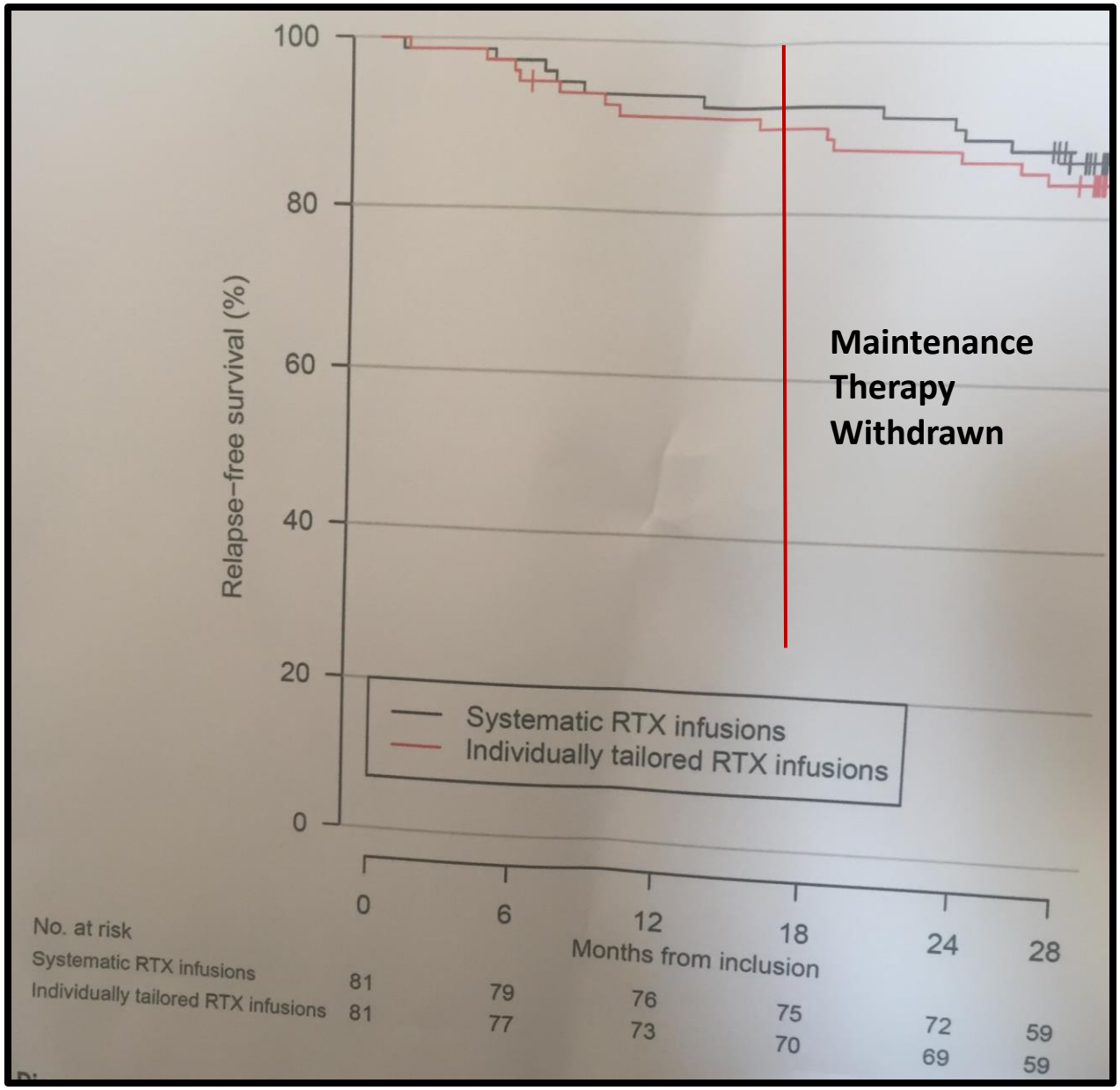
Guilliven et al, N Eng J Med, 2014

A First Look at MAINRITSAN 2 Results

After induction of remission was achieved with corticosteroids and an immunosuppressive agent patients were randomized to:

Systematic RTX: 500mg on D1 and D15 followed by 500 mg every 6 months through month 18

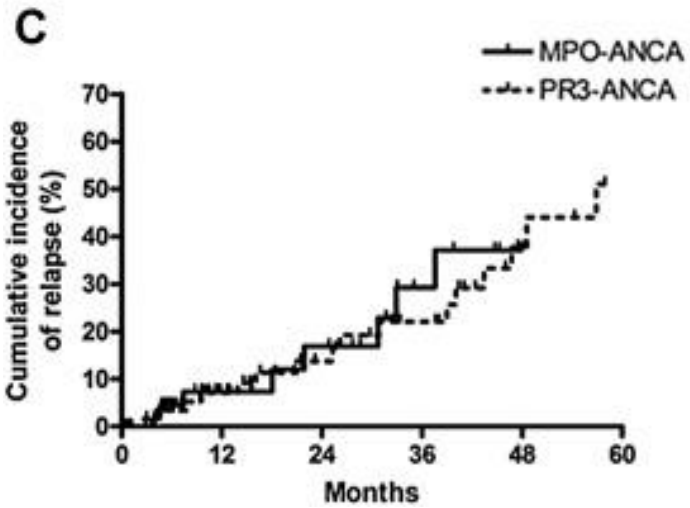
Tailored RTX: 500 mg on D1 followed by an examination of ANCA status and B Cell counts every three months; RTX was redosed (500mg) if B cells became > 0/mm³ or if ANCA went from negative to positive or if ANCA titers increased



French Vasculitis Study Group, Presented at the 2017 AAV International Meeting, Tokyo

What is the Duration of Maintenance Immunosuppression?

- **Unclear, but may be answered by the REMAIN study of short or long courses of AZA**
- **Patients on dialysis with no recovery after 3 months and no other systemic involvement may no longer need maintenance**
- **It has been suggested that MPO-ANCA patients may not need maintenance as relapse rate is far less than PR3-ANCA, but…**

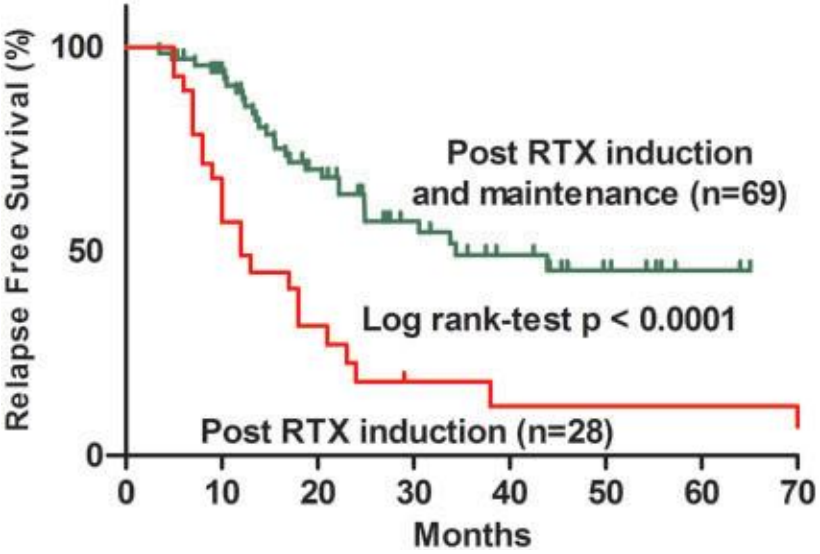


In a cohort of 126 patients with AAV and rapidly progressive renal deterioration treated with PLEX in addition to corticosteroids and immunosuppression, the relapse rate for MPO and PR3-ANCA was the same

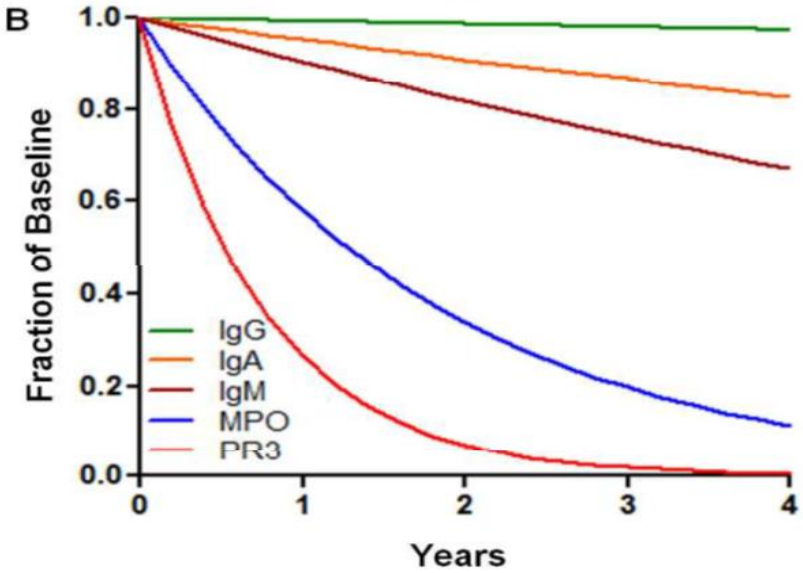
Kemma et al, J Am Soc Nephrol, 2015; de Luna et al, J Autoimmunity, 2015

How Long Should Rituximab be Given for Maintenance?

- Even after induction with rituximab and maintenance for 2 years with fixed-interval rituximab, relapses began occurring after stopping the rituximab (green line)



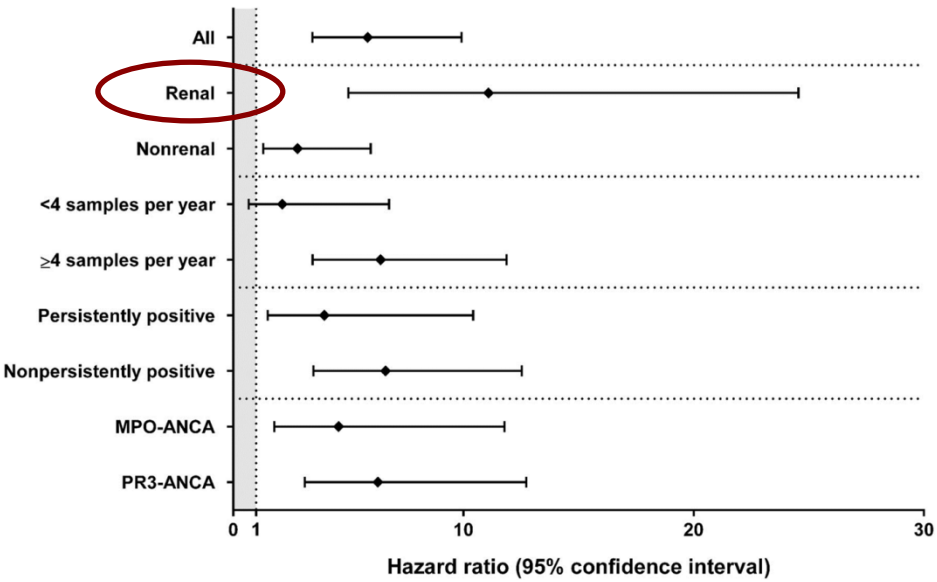
- Patients were kept on fixed-interval maintenance with rituximab, median follow-up 2.4 years but with some patients over 7 years
- ANCA declined more rapidly then IgG, A or M
- Hypogammaglobulinemia developed mainly in those who entered maintenance with a median IgG of 448 mg/dL
- Infections were 0.85/10 patient years
- Risk of infection related to age and IgG <400 mg/dL
- It appears rituximab can be given long-term safely



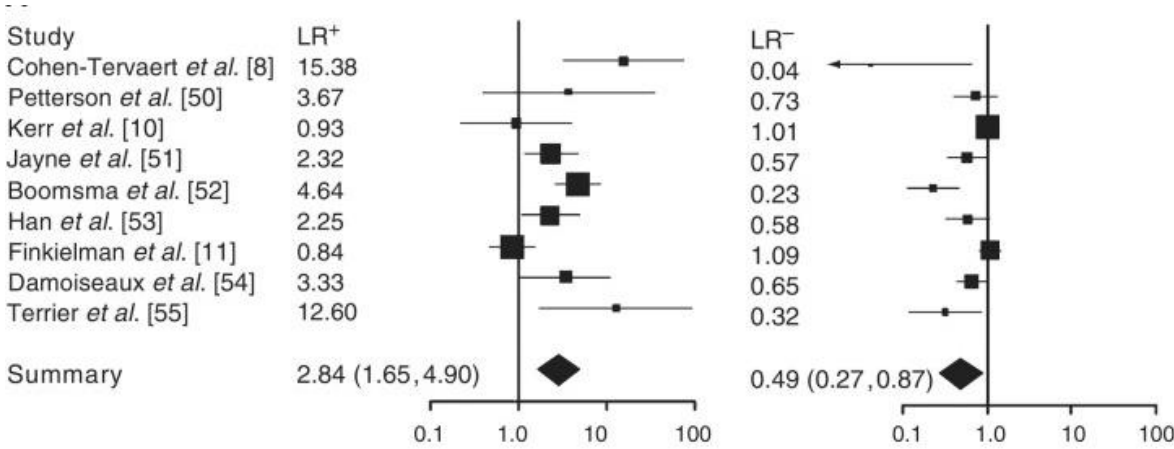
Alberici et al, Rheumatol, 2015; Cortazar et al, Arth Rheumatol, 2016

Predicting Relapse by Increasing ANCA Titers

- 166 patients
- Followed 49±33 months
- ANCA rises occurred an average of 20±17 months after last disease activity
- Half the relapses occurred within 18 months of ANCA rise
- All patients who became ANCA negative had an ANCA rise before a major relapse
- Fewer than half the patients with an ANCA rise relapsed within a year of the rise



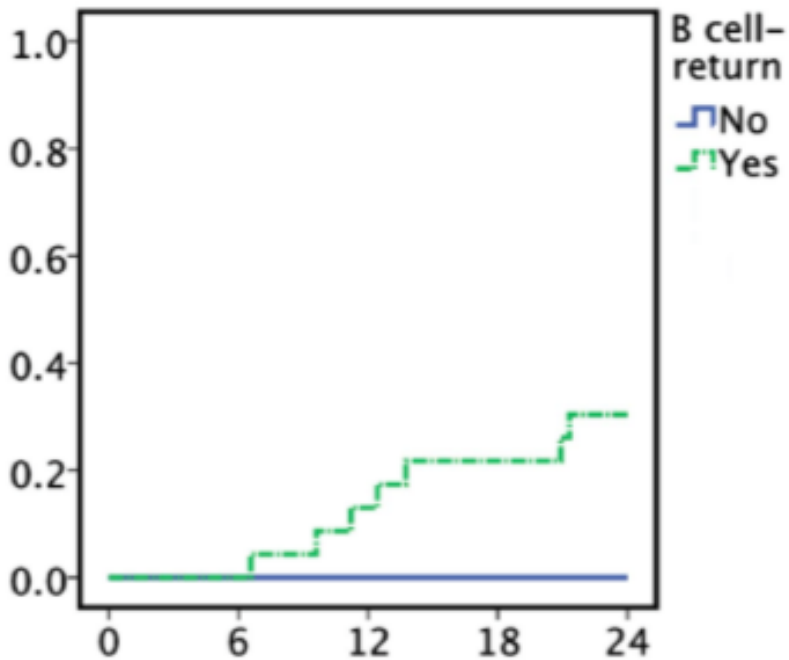
- A meta-analysis of the ability of a rising ANCA titer to predict disease relapse
- Overall a modest effect with a likelihood ratio of 2.84
- Studies with higher proportion of patients with kidney disease or other severe manifestations had higher likelihood ratios



Kemma et al, J Am Soc Nephrol, 2015; Tomasson et al, Rheumatol, 2012

Predicting Relapse by Return of B Cells

- **In many studies using rituximab for AAV, patients do not experience a relapse unless B cells have returned**



Relapse rate in the Rituximab group stratified on the basis of B cell return

- **One study found that the type of B cells at reconstitution was important**
- **Low CD5+ B cells, a surrogate for B regulatory cells was associated with relapse with a HR=3.7, P<0.01 after adjusting for PR3-ANCA and upper respiratory involvement**
- **Similarly, relapse rates were lower if more naïve B cells are present at reconstitution; it has been speculated that B regulatory cells are in the naïve population**

Jones et al, Ann Rheum Dis, 2015; Bunch et al, Ann Rheum Dis, 2015; Yusof et al, Ann Rheum Dis, 2015

Clinical Interpretation-Biomarkers of Relapse

- **If a patient becomes ANCA negative and remains negative, risk of relapse is low**
- **An ANCA rise in a patient with AAV and renal involvement should put physicians on alert that a relapse may occur**
- **May not be worth measuring serial ANCA levels in non-renals**
- **In rituximab-treated patients relapse rate is low in the absence of a return of B cells**
- **In rituximab-treated patients relapses may be higher if B cells return, but there are fewer regulatory B cells**
- **A rise in ANCA or a return of B cells (in a rituximab-treated patient) does not mean pre-emptive treatment should be initiated, but rather patients should be followed carefully because they could relapse**