Updates on vasculitis and rituximab

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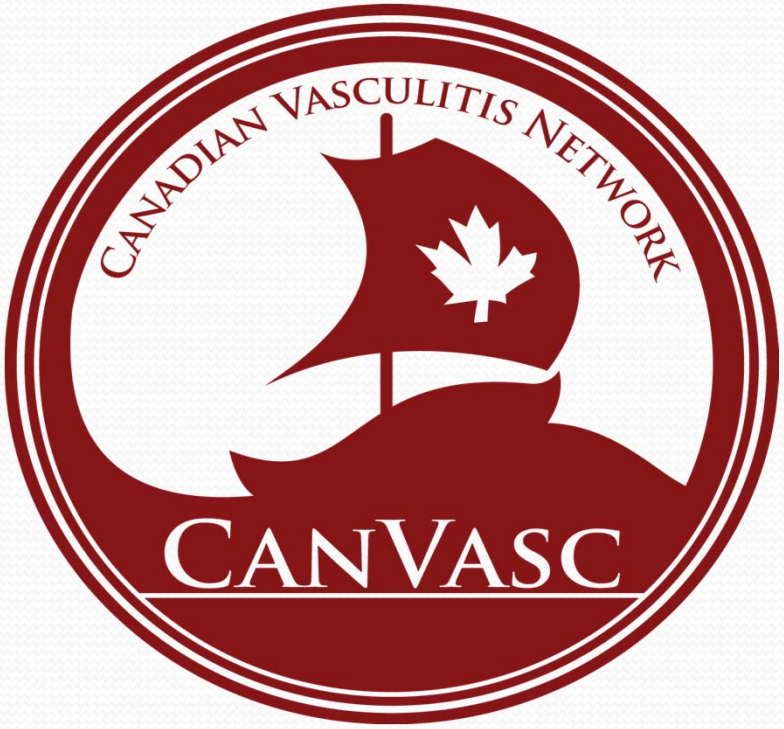
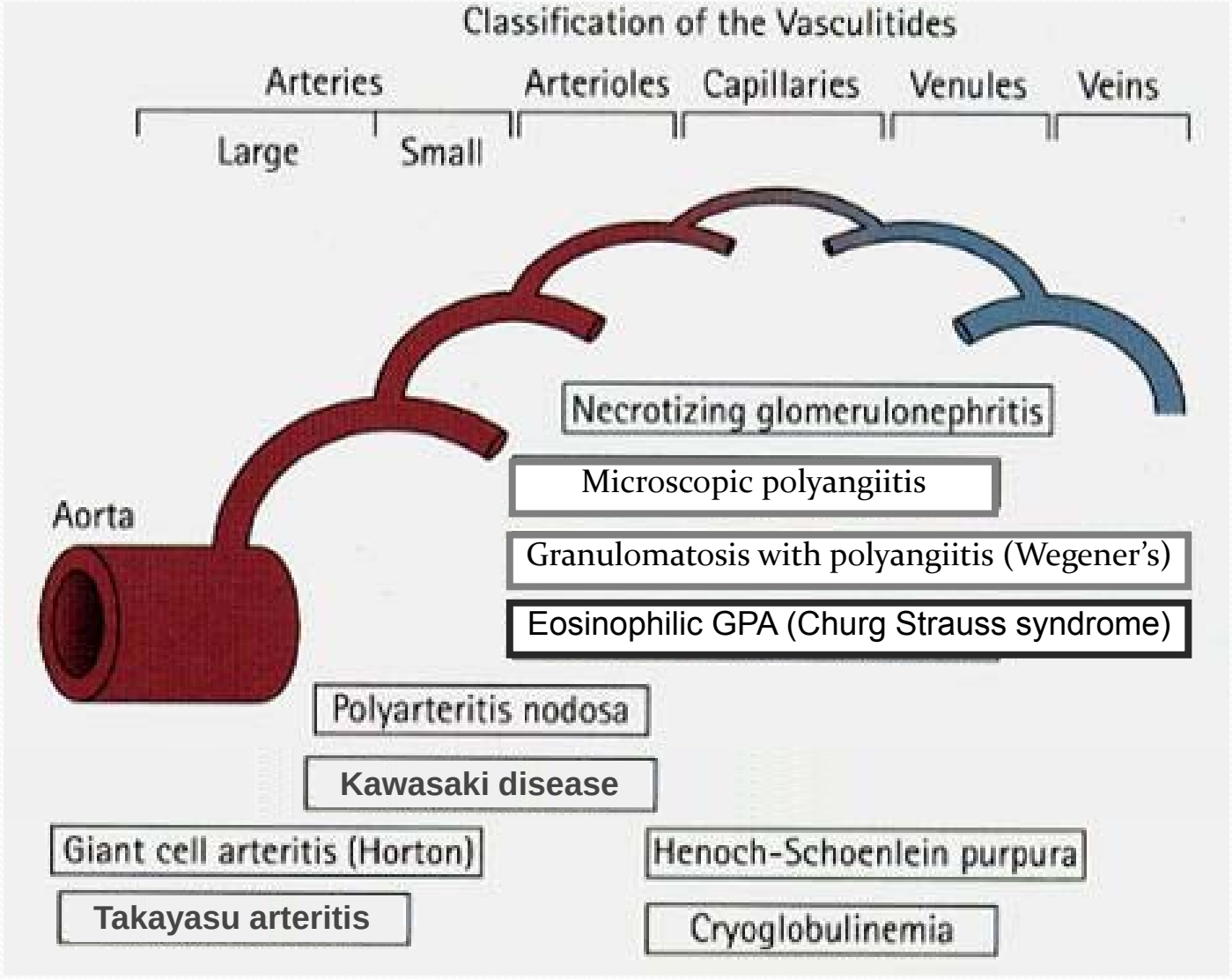
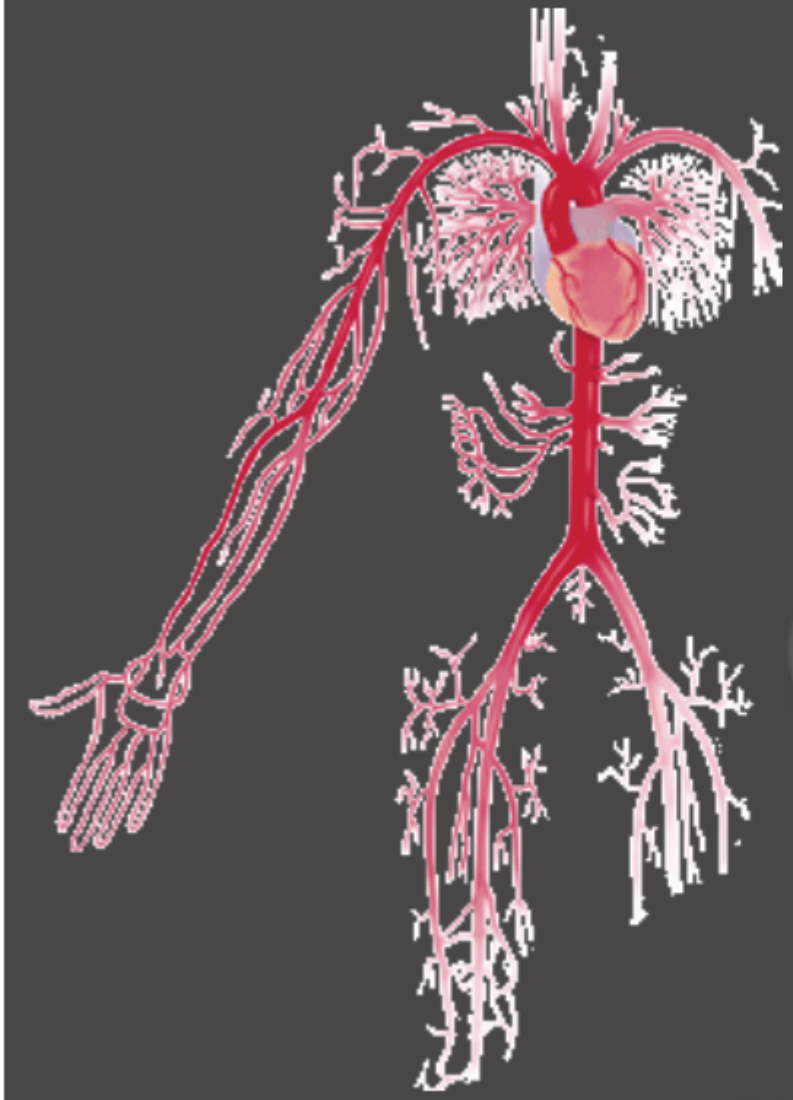




Jennette et al. Arthritis Rheum 1994;37:187-92
Falk et al. Arthritis Rheum 2011 Apr;63(4):863-4



DCVAS

Diagnostic and Classification Criteria for Systemic Vasculitis

STUDY OVERVIEW

2012 revised Chapel hill nomenclature

- **Large Vessel Vasculitis (LVV):** Takayasu Arteritis (TAK) and Giant Cell Arteritis (GCA)
- **Medium Vessel Vasculitis (MVV):** Polyarteritis Nodosa (PAN) and Kawasaki Disease (KD)
- **Small Vessel Vasculitis (SVV):**
  - *ANCA-Associated Vasculitis (AAV)*: Microscopic Polyangiitis (MPA), Granulomatosis with Polyangiitis (Wegener's) (GPA) and Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss) (EGPA)
  - *Immune Complex SVV:* Anti-GBM Disease, Cryoglobulinemic Vasculitis, IgA Vasculitis (Henoch-Schönlein) (IgAV) and Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis) (HUV).

2012 revised Chapel hill nomenclature

- **Variable Vessel Vasculitis (VVV):** Behçet's Disease (BD) and Cogan's Syndrome (CS).
- **Single Organ Vasculitis (SOV):** Cutaneous Leukocytoclastic Angiitis, Cutaneous Arteritis, Primary CNS Vasculitis and Isolated Aortitis.

- **Vasculitis Associated with Systemic Disease:** Lupus Vasculitis, Rheumatoid Vasculitis and Sarcoid Vasculitis.

- **Vasculitis Associated with Probable Etiology:** Hepatitis C Virus-Associated Cryoglobulinemic Vasculitis, Hepatitis B Virus-Associated Vasculitis, Syphilis-Associated Aortitis, Serum Sickness-Associated Immune Complex Vasculitis, Drug-Associated Immune Complex Vasculitis, Drug-Associated ANCA-Associated Vasculitis and Cancer-Associated Vasculitis.

Vasculitis and rituximab

- **Large Vessel Vasculitis (LVV):** Takayasu Arteritis (TAK) and Giant Cell Arteritis (GCA)
- **Medium Vessel Vasculitis (MVV):** Polyarteritis Nodosa (PAN) and Kawasaki Disease (KD)
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- **Variable Vessel Vasculitis (VVV):** Behçet's Disease (BD) and Cogan's Syndrome (CS).
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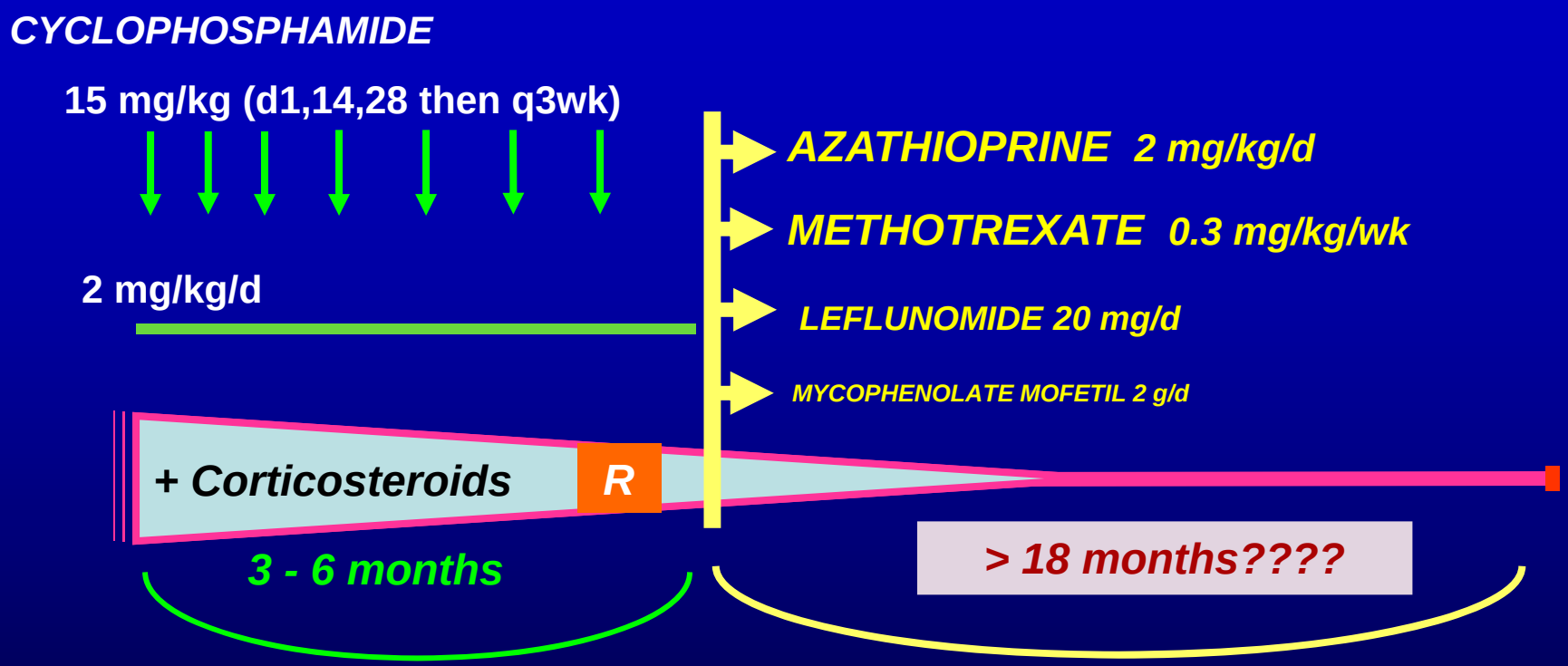
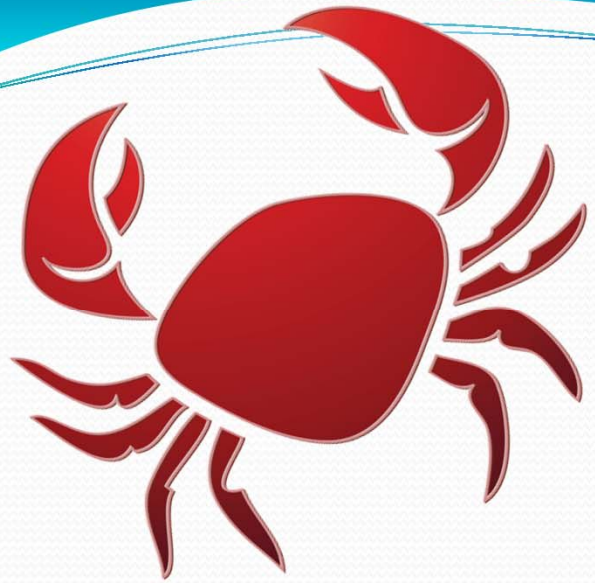
Treatment of severe GPA/MPA



+ adjuvant/prophylactic measures: cotrimoxazole, osteoporosis treatment, etc



Frequent relapses…

	Patients		Follow-up from Dg	Relapse rate	p
CYCAZAREM NEJM, 2003	WG, MPA	144	18 mo	AZA 15,5% vs. CYC 13,7%	NS
WGET NEJM, 2005	WG	180	27 mo	MTX 32,8% vs MTX/ETN 30,6%	NS
Langford Am J Med, 2003	WG	42	35 mo	52%	
WEGENT **Pagnoux, NEJM, 2009**	WG, MPA	126	37,3 mo	AZA 36,5% vs MTX 33,3%	NS
Sanders NEJM, 2003	WG, MPA	136	→ 5 yrs	AZA 42.3% vs. CYC 57.4%	NS

At 7 years, relapse rate 63.9% → 51.2% (445 patients)

Holle et al. Arthritis Rheum 2011 Jan;63(1):257-66

Table 1. Rituximab use in ANCA-associated vasculitis: review of published case series and cohort studies

Study	Study design	Patient number/diagnosis	RTX doses (patient[d] – doses[d] × amount)	Concomitant drugs	Remission	Follow-up (months)	Relapse ([d])
Keogh *et al.* [32]	Case series	10 GPA; 1 MPA	11–4 × 375 mg/m^2	11 GCS	11 complete	14 median	2
Keogh *et al.* [33]	Prospective pilot study	10 GPA	10–4 × 375 mg/m^2	10 GCS	10 complete	12 median	1
Eriksson [34]	Prospective	7 GPA; 2 MPA	6–4 × 500 mg; 2–2 × 500 mg; 1–4 × 375 mg/m^2	2 CYC; 4 MMF; 1 MMF + SIR; 1 AZA; 1 None	8 complete; 1 partial	19 median	2
Omdal *et al.* [35]	Case series	3 GPA	2–4 × 375 mg/m^2; 1–1 × 375 mg/m^2	Unknown	3 complete	12 median	3
Aries *et al.* [36]	Prospective pilot study	8 GPA	8–4 × 375 mg/m^2 q4 weeks	5 CYC; 2 MTX; 1 MMF	2 complete; 1 partial; 5 failed	18 median	0
Gottenberg *et al.* [37]	Case series	2 GPA	1–3× 375 mg/m^2; 1–15× 375 mg/m^2	1 MP; 1 MTX + MMF	1 complete; 1 failed	16.5 median	0
Stasi *et al.* [38]	Prospective long-term	8 GPA; 2 MPA	10–4 × 375 mg/m^2	GCS	9 complete; 1 partial	33.5 median	3
Smith *et al.* [39]	Prospective long-term	5 GPA; 5 MPA; 1 EGPA	11–4 × 375 mg/m^2	11 CYC; (1 dose)	9 complete; 1 partial; 1 failed	23 median	5
Brihaye *et al.* [40]	Case series	8 GPA	7–4 × 375 mg/m^2; 1–2 × 1 g	4 MTX; 3 MMF; 1 AZA; 5 GCS	3 complete; 3 partial; 2 failed	Unknown	1
Henes *et al.* [41]	Case series	6 GPA	6–4 × 375 mg/m^2	4 GCS; 5 Leflunomide	5 complete; 1 partial	16 mean	1
Garcia-Hernandez *et al.* [42]	Case series	4 GPA	4–4 × 375 mg/m^2	4 GCS; 4 CYC	1 complete	12.3 median	1
Ramos-Casals *et al.* [43]	Case series	17 GPA; 2 MPA	18–4 × 375 mg/m^2; 1–2 × 1 g	19 GCS; 12 other (not specified)	10 complete; 3 partial; 6 failed	31 mean	9
Seo *et al.* [44]	Case series	8 GPA (limited disease)	8–4 × 375 mg/m^2	8 GCS; 1 CYC	8 complete	NR	5
Tamura *et al.* [45]	Case series	2 GPA	2–4 × 375 mg/m^2	2GCS	2 complete	12 and 6	1
Mansfield *et al.*[a] [46]	Prospective; Long-Term	13 GPA; 10 MPA	23–2 × 1 g	23 GCS; 23 CYC	22 complete; 1 failed	39 median	5
Sanchez-Cano *et al.* [47]	Case series	4 GPA	4–4 × 375 mg/m^2	4 GCS; 3 MTX; 1 CYC	2 complete; 2 partial	18.7 mean	2
Roccatello *et al.* [48]	Case series	4 MPA; 2 GPA; 1 EGPA	7–4 × 375 mg/m^2	7 GCS; 1 MMF; 1 MTX	7 complete	12 median	0
Lovric *et al.* [49]	Case series	13 GPA; 1 MPA; 1 EGPA	15–4 × 375 mg/m^2	15 GCS; 1 CYC; 6 AZA; 1 cyclosporine; 1 MTX; 1 Infliximab	6 complete; 8 partial; 1 failed	15 median	3
Jones *et al.* [50]	Case series	42 GPA; 10 MPA; 5 EGPA; 3 unclassified	26–4 × 375 mg/m^2; 32–2 × 1 g; 7 Other	28 CYC; 17 GCS	49 complete; 15 partial; 1 failed	20 median	28
Eleftheriou *et al.*[b] [51]	Case series	4GPA	3–2 × 750 mg/m^2; 1–4 × 375 mg/m^2	3 CYC; 1 MMF	Not specified	32 median	NR
Taylor *et al.*[c] [52]	Case series	10 GPA	10–2 × 1 g	10 GCS; 3 MMF; 1 CYC; 2 MTX; 2 AZA	10 complete	12 median	0
Roccatello *et al.* [53]	Case series	5 GPA; 4 MPA; 2 EGPA	11–4 × 375 mg/m^2	11 GCS[d]	11 complete	30 median	2

Rodrigo Cartin-Ceba, ***Curr Opin Rheum 2012; 24***

Jones et al 2009

A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis.

Arthritis Rheum 2009
60(7):2156-68

ARTHRITIS & RHEUMATISM
Vol. 60, No. 7, July 2009, pp 2156–2168
DOI 10.1002/art.24637

A Multicenter Survey of Rituximab Therapy for Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Rachel B. Jones,[1] Alastair J. Ferraro,[2] Afzal N. Chaudhry,[1] Paul Brogan,[3] Alan D. Salama,[4] Kenneth G. C. Smith,[5] Caroline O. S. Savage,[2] and David R. W. Jayne[1]

Objective. **B cell depletion with rituximab has allowed remissions in relapsing or refractory antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis in small studies. The aim of this study was to determine the efficacy and safety of rituximab for ANCA-associated vasculitis in a larger multicenter cohort. This permitted comparison of rituximab dosing regimens, the value of continuing immunosuppression, and investigation of ANCA and B cell levels as re-treatment biomarkers.**

Methods. **Retrospective, standardized data collection from 65 sequential patients receiving rituximab for refractory ANCA-associated vasculitis at 4 centers in the UK was used.**

Results. **All patients achieved B cell depletion. Complete remission occurred in 49 of the 65 patients (75%), partial remission in 15 (23%), and no response in 1 (2%). The prednisolone dosage was reduced from 12.5 mg/day (median) to 9.0 mg/day at 6 months (P = 0.0006). Immunosuppressive therapy was withdrawn in 37 of 60 patients (62%). Twenty-eight of 49 patients who achieved full remission (57%) experienced relapse (median 11.5 months). B cell return preceded relapse in 14 of 27 patients (52%). Although ANCA levels fell after rituximab therapy, relapse was not associated with ANCA positivity or a rise in ANCA levels. Neither the initial rituximab regimen (4 infusions of 375 mg/m^2 each given 1 week apart or 2 infusions of 1 gm each given 2 weeks apart) nor withdrawal of immunosuppressive therapy (37 of 60 patients [62%]) influenced the timing of relapse. Thirty-eight patients received ≥2 courses of rituximab, and complete remission was induced or maintained in 32 of them (84%). IgM levels fell, although IgG levels remained stable. Forty-six serious adverse events occurred, including 2 episodes of late-onset neutropenia, which were attributed to rituximab.**

Conclusion. **Rituximab was effective remission induction therapy for refractory ANCA-associated vasculitis in this study. There was no difference in efficacy between the 2 main treatment regimens. Continuing immunosuppression did not reduce relapses. Relapses occurred, but re-treatment was effective and safe. There was no clear influence of rituximab on the frequency of serious adverse events. ANCA and B cell levels lacked sufficient sensitivity to guide the timing of re-treatment.**

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis is a multisystem autoimmune disease characterized by ANCA production and small-vessel inflammation. The ANCA-associated vasculitides comprise Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS), which have similar clinical and serologic features and similar treatment responses.

Standard immunosuppressive therapies for

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Dr. Salama has received consulting fees, speaking fees, and/or honoraria from Roche and Novartis (less than $10,000 each). Dr. Smith has received an honorarium from Roche for attending an Advisory Board meeting (less than $10,000). Dr. Savage has received consulting fees from Talecris Biotherapeutics and Biovitrum and speaking fees from Roche (less than $10,000 each). Dr. Jayne has received consulting fees, speaking fees, and/or honoraria from Roche concerning rituximab (less than $10,000), as well as research grant support from Roche for investigator-initiated studies.

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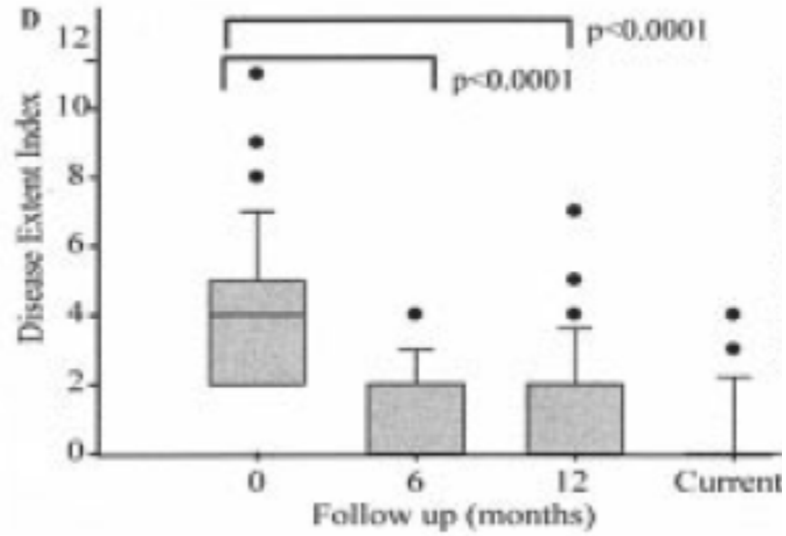
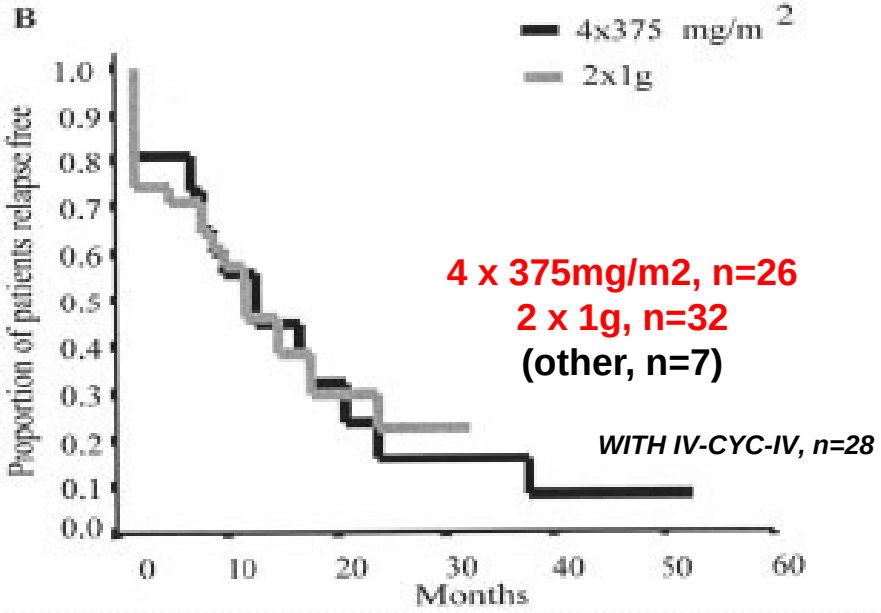
Table 1. Characteristics and treatments in the patients with ANCA-associated vasculitis, by rituximab treatment group*

	Rituximab protocol			
	Two infusions of 1 gm each given 2 weeks apart (n = 32)	Four infusions of 375 mg/m^2 each given 1 week apart (n = 26)	Other (n = 7)†	All patients (n = 65)
Patient characteristics				
Age at first rituximab course, years	49 (16–77)	47 (11–69)	25 (7–56)	47 (7–77)
No. (%) male	16 (50)	13 (50)	5 (71)	34 (52)
Diagnosis, no. of patients	WG in 26, MPA in 4, CSS in 2	WG in 16, MPA in 6, CSS in 3, unclassified in 1	WG in 4, unclassified in 3	WG in 46, MPA in 10, CSS in 5, unclassified in 4
History of ANCA by diagnosis, no. of patients	PR3 in 21, MPO in 2, cANCA in 2, pANCA in 1	PR3 in 11, MPO in 5, cANCA in 5, pANCA in 1	PR3 in 5, cANCA in 1, MPO in 1	PR3 in 37, MPO in 8, cANCA in 8, pANCA in 2
Disease duration before rituximab, months	72 (2–288)	84 (10–360)	60 (7–216)	72 (1.5–360)
Cumulative CYC dose (oral plus IV), gm	28 (1–150)	17 (0–90)	15 (0–100)	24 (0–150) (2 patients took no CYC)
Previous immunotherapy, no. (%)				
Anti-TNFα	11 (34)	8 (31)	5 (71)	24 (38)
IVIG	6 (19)	10 (38)	1 (14)	17 (26)
Azathioprine	26 (81)	17 (65)	6 (86)	49 (77)
Methotrexate	10 (31)	4 (15)	4 (57)	18 (28)
Mycophenolate mofetil	23 (72)	19 (73)	5 (71)	47 (74)
Other	10 (31)	13 (50)	2 (29)	25 (38)
Total no. of previous therapies/patient	4 (2–8)	4 (2–8)	4 (2–6)	4 (2–8)
No. of previous relapses/patient	3 (1–16)	3 (2–11)	6 (5–7)	3 (1–16)
ANCA status at study entry by diagnosis, no. of patients	PR3 in 13, MPO in 1, cANCA in 1	PR3 in 8, MPO in 5, cANCA in 1	PR3 in 4	PR3 in 25, MPO in 6, cANCA in 2, negative in 32
Total followup after rituximab, months	21 (3–39)	17 (3–52)	21 (12–40)	20 (3–55)

15% have always been tested ANCA negative

Jones R, Arthritis Rheum 2009;60:2156-68





4 x 375mg/m2, n=26
2 x 1g, n=32
(other, n=7)

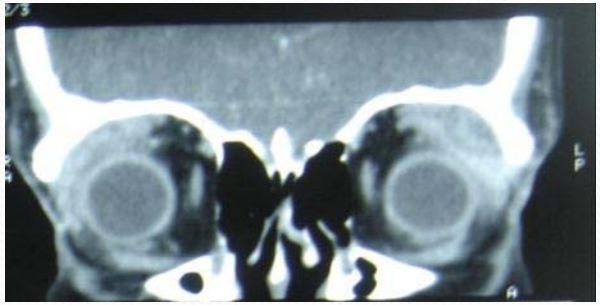
WITH IV-CYC-IV, n=28

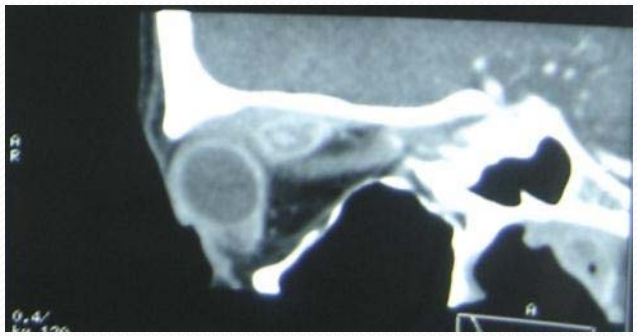
CR 49/65 (75%) and PR 15/65 (23%) at M2 (mean)

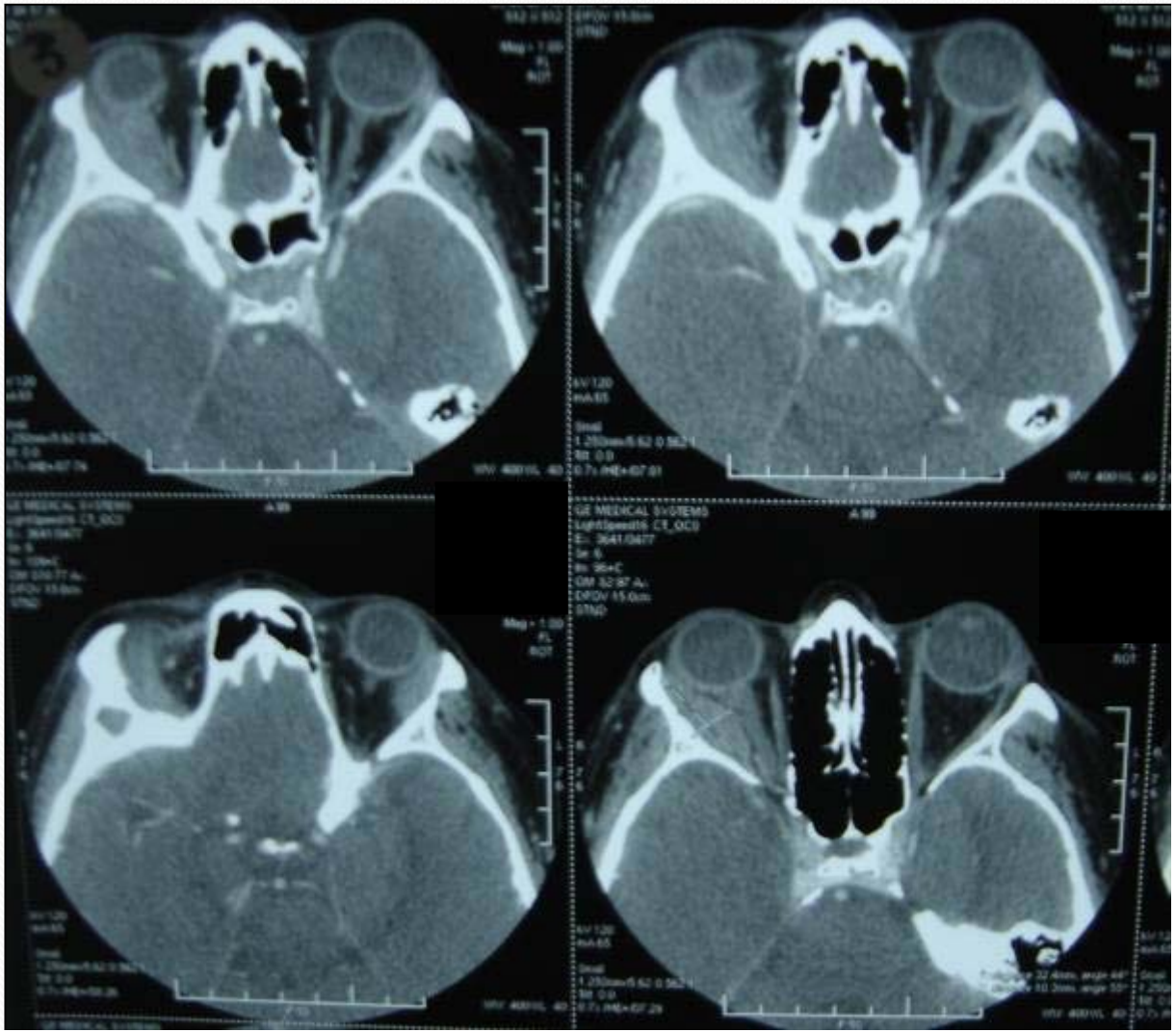
(15 still in CR at M21 after 1 single course)

1 failure = granulomatous orbital tumor

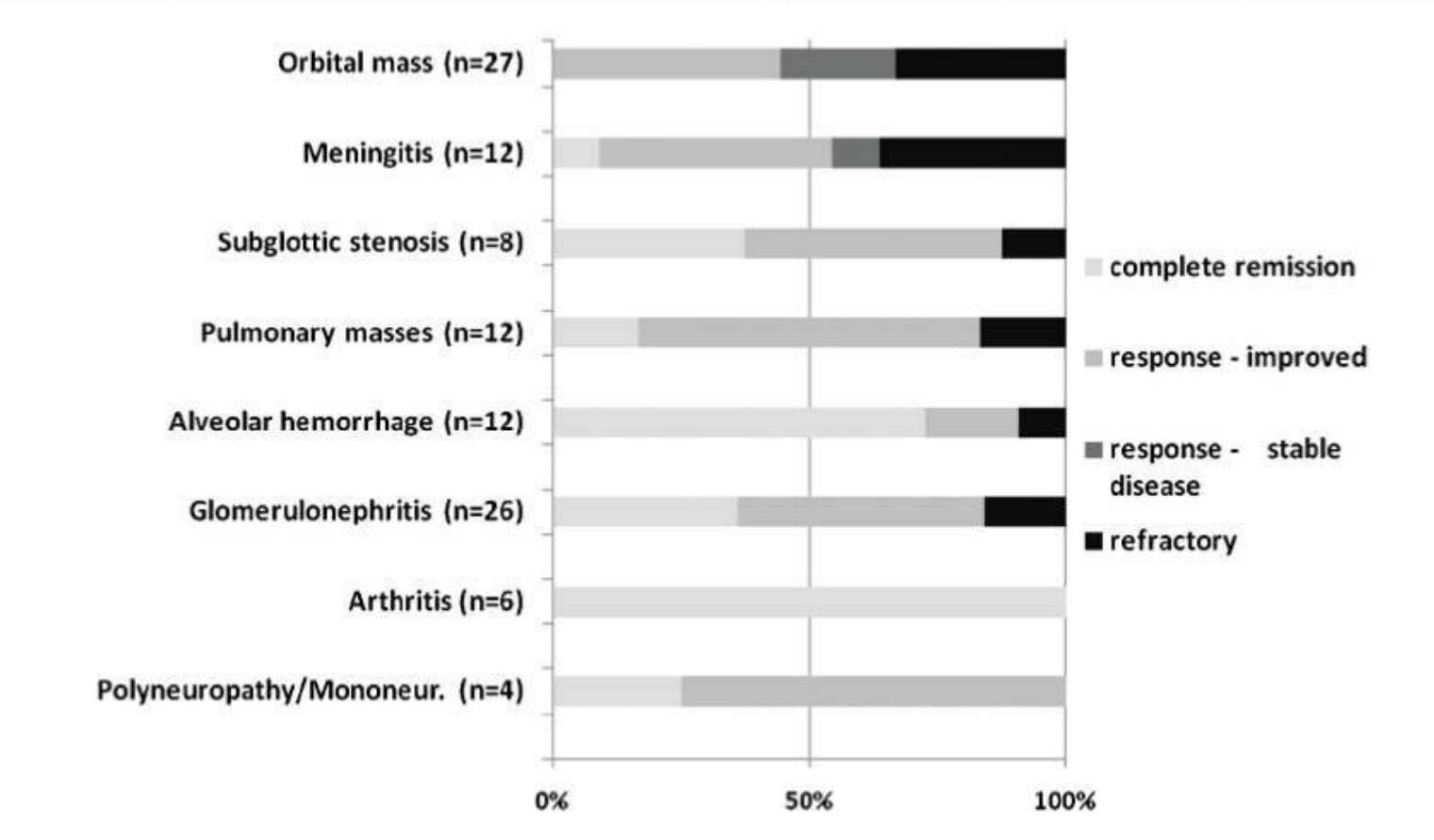
Jones R, Arthritis Rheum 2009;60:2156-68







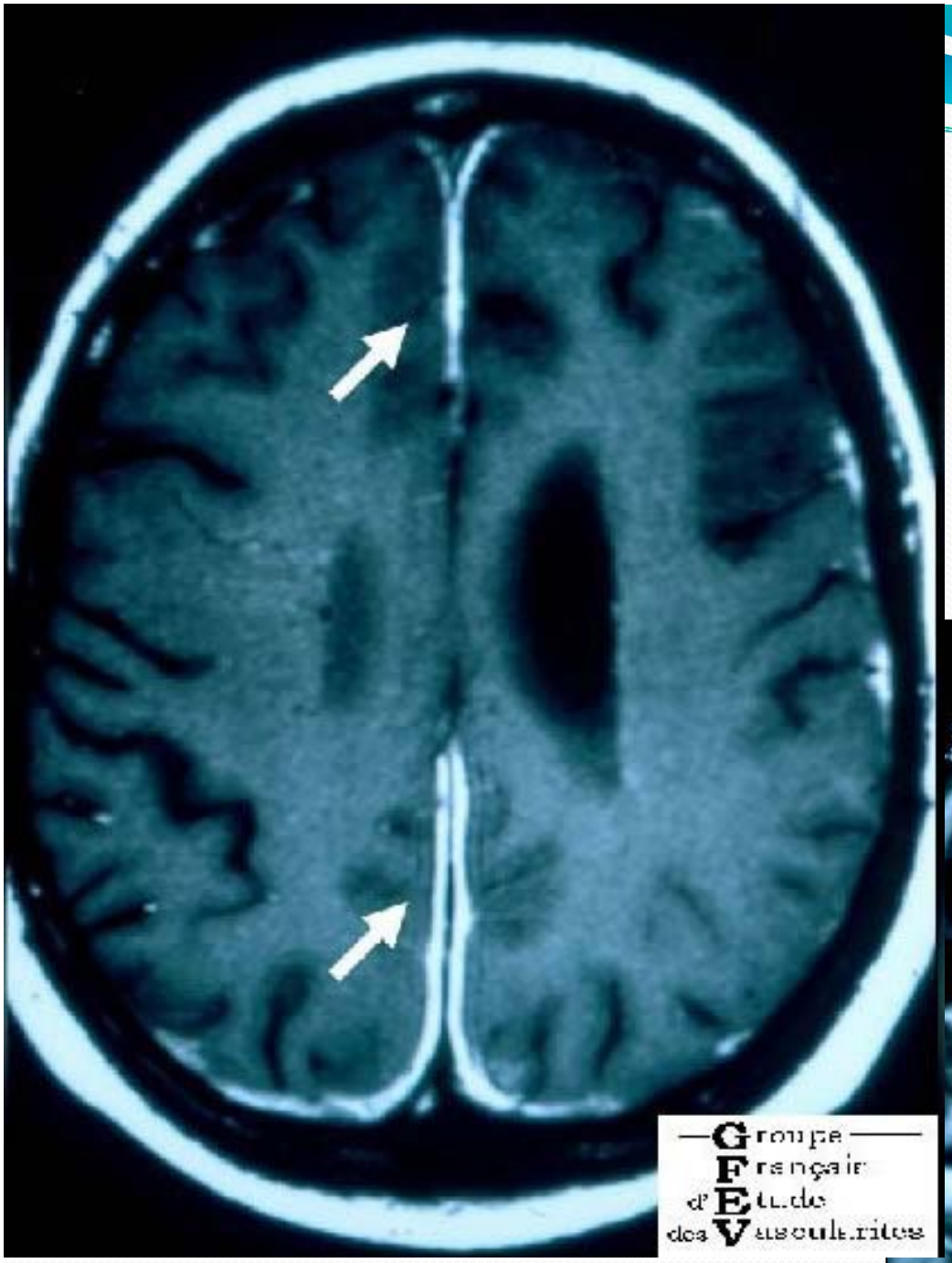
Different responses to rituximab



59 patients, 2002-2010

26.7% of refractory disease!!!

Holle et al, Arthritis Rheum 2012 Mar;71(3):327-33.


Groupe
Français
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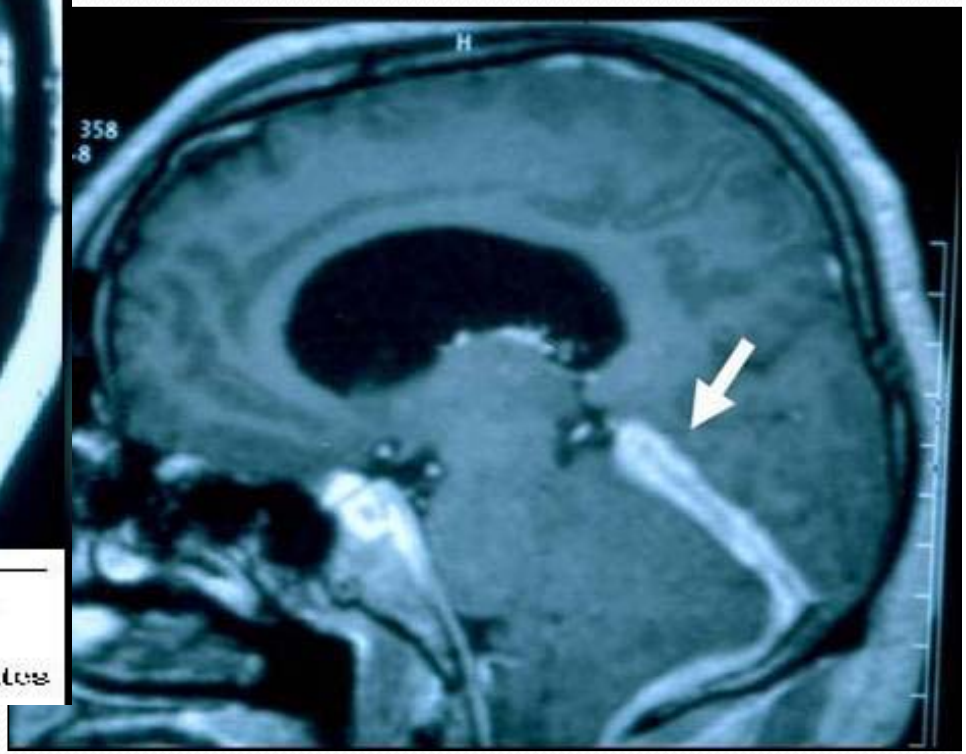
des Vascularites


H
358
-8

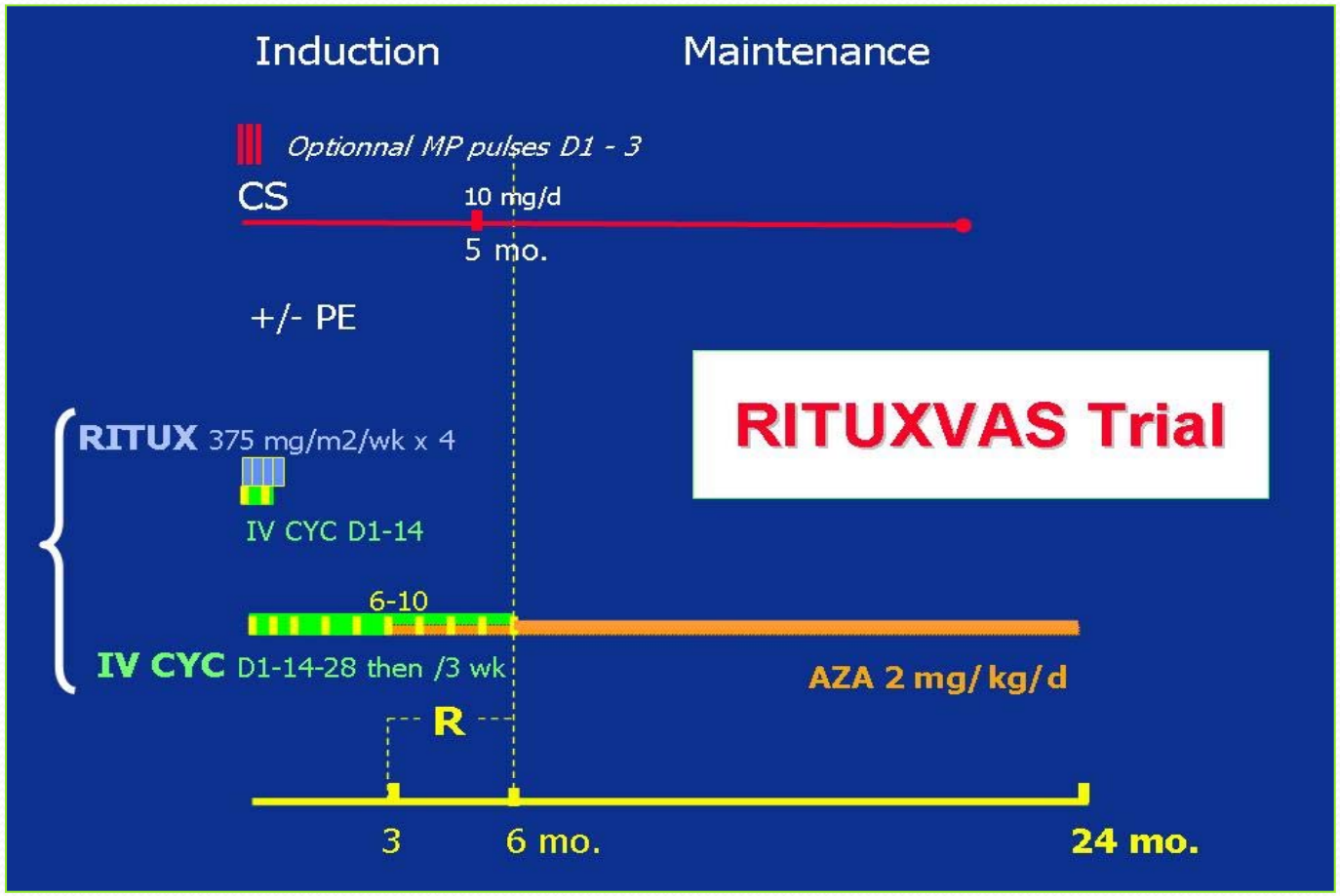
Adverse events

- 45 SAE in 25 patients
- 16 severe infections at M8
- 1 death because of vasculitis
- 1 sudden death at M3, in CR
- 2 delayed neutropenias at M3 M5, no sepsis
- 2 asthma flares

- Decrease in Ig M (n patients ??) from 0.28 to 0.3 g/l
- IgG stable

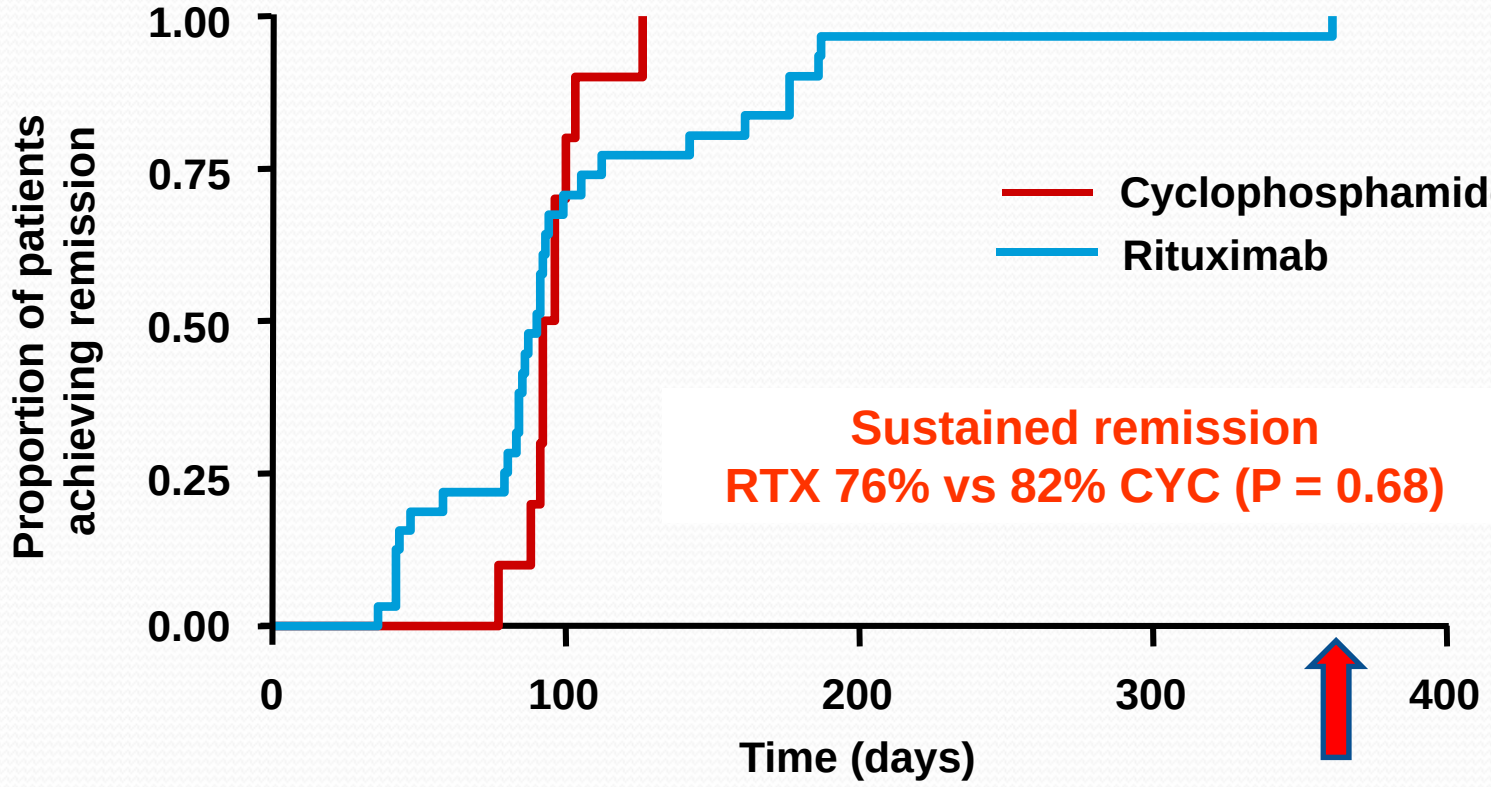
Jones R, Arthritis Rheum 2009;60:2156-68

ANTI CD20


Induction
Maintenance
Optionnal MP pulses D1 - 3
CS
10 mg/d
5 mo.
+/- PE
RITUX 375 mg/m2/wk x 4
IV CYC D1-14
RITUXVAS Trial
6-10
IV CYC D1-14-28 then /3 wk
AZA 2 mg/ kg/ d
R
3
6 mo.
24 mo.

Rituximab versus cyclophosphamide: Patients achieving remission

n=44 patients with new disease with renal involvement
BVAS 0 maintained for 6 months



Jones R for the EUVAS, *N Engl J Med* 2010;363(3):211-20

RAVE

(<350 µM)
(no severe AH)
ANCA+

1 à 3 MP pulse(s)

CS + **oral CYC** * 3 to 6 mo

+ placebo RTX

Rituximab + CS**

+ placebo CYC

AZA → M18

Placebo AZA

* oral CYC 2 mg/kg/d

** **RTX 375 mg/m2 x 4**

Primary endpoint

CR at 6 mo (BVAS/WG = 0 & **prednisone = 0 mg**)

	RTX (n=99)	CYC (n=98)	Difference	*P*
N (%)	**63 (63.6%)**	**52 (53.1%)**	**10.6%**	**0.09**
95% IC	54.1-73.2%[2]	43.1-63.0%[2]	(–3.2) -24.3%[1]	

Intent-to-treat analysis (ITT), with “worst case imputation”

Stone J et al. *N Engl J Med*. 2010;363:221-232

Adverse events at 6 months

	RTX (n=99)	CYC (n=98)	*P*
Total no. of AEs	**31**	**33**	
No. (%) of patients with >1 AE	22 (22%)	32 (33%)	0.01
No. of patient-month	569.3	561.3	
Annual rate of AEs per patient	5%	6%	0.285

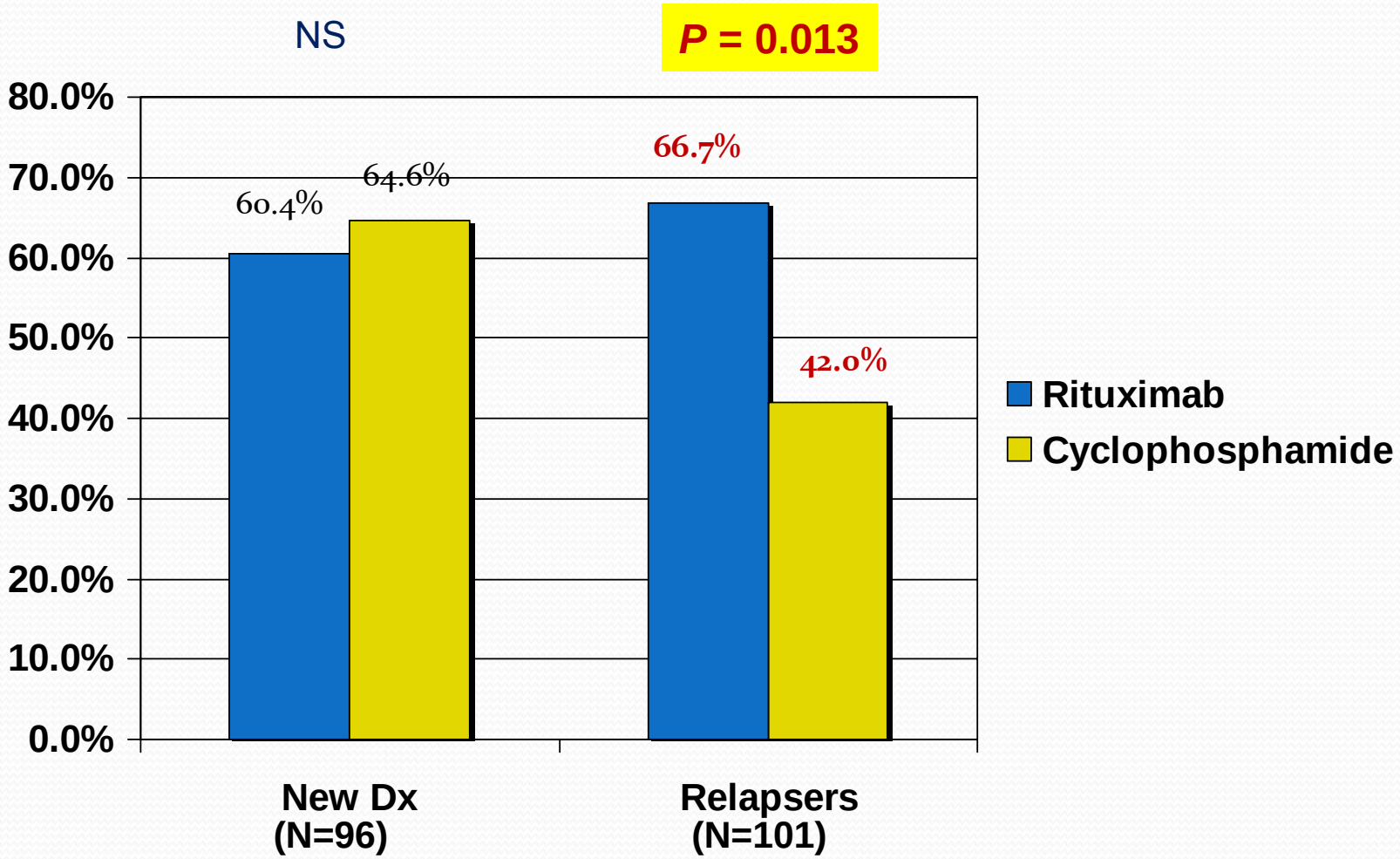
Stone J et al. *N Engl J Med*. 2010;363:221-232

Alveolar Hemorrhage Subset

	Rituximab (N=99)	Cyclophosphamide (N=98)
Alveolar hemorrhage at BL	**27 (27.3%)**	**23 (23.5%)**
Achieved primary outcome	59.3 %	47.8%
BVAS/WG = 0, Pred<10 mg	**70.4 %**	**60.9%**
Early Treatment Failure	**3**	**1**
Crossover	**2**	**1**
Death by 6 month	**1**	**0**

Presented ACR 2010;Specks U,Stone J.

Better response in relapsers
(vs newly-diagnosed)



Stone JH et al, *N Engl J Med* 2010;363(3):221-32

UK recommendations for the use of rituximab in ANCA-associated vasculitides

A group of 11 vasculitis experts from the UK, including 5 nephrologists and 1 pediatrician (DELPHI exercise, systematic review of the literature, categorization of evidence)
Results of studies on rituximab published in 2010 and 2011 have not been included

Recommendation 1			Level of evidence
	What are the indications for rituximab as a treatment of ANCA-associated vasculitis?		
		In newly diagnosed ANCA-associated vasculitis: Rituximab is as effective as CYC for remission inductionof previously untreated patients. Rituximab may be preferred, especially when CYC avoidance is desirable.	1b
		In refractory and/or relapsing disease: Rituximab is an effective treatment of refractory and/or relapsing forms of ANCA-associated vasculitis and can be recommended when conventional therapy has failed.	1b
		According to patient subgroups • WG with head and neck manifestations: Rituximab is an effective treatment of refractory head and neck manifestations of WG and can be recommended when conventional therapy has failed.	2b/4
		• Paediatric ANCA-associated vasculitis: Rituximab should be considered for the treatment of children with ANCA-associated vasculitis that fails to respond to conventional induction therapy with glucocorticoids and CYC; or for patients with relapsing disease where there is particular concern regarding cumulative glucocorticoid and/or CYC toxicity.	4
		• Churg-Strauss syndrome: Response rates in refractory and/or relapsing: Churg-Strauss syndrome appear similar to other vasculitides and rituximab may be considered when conventional therapy has failed.	4

Guerry et al. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2011

Rituximab for ANCA vasculitis

- Approved by the FDA for severe forms of GPA and MPA in adults and in combination with corticosteroids

APRIL 2011

HC DEC. 2011

Ontario APR. 2012

REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:

a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
b) The patient has failed three months of oral cyclophosphamide therapy; OR
c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
d) Cyclophosphamide is contraindicated; OR
e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
f) The patient wishes to preserve ovarian/testicular function for fertility.

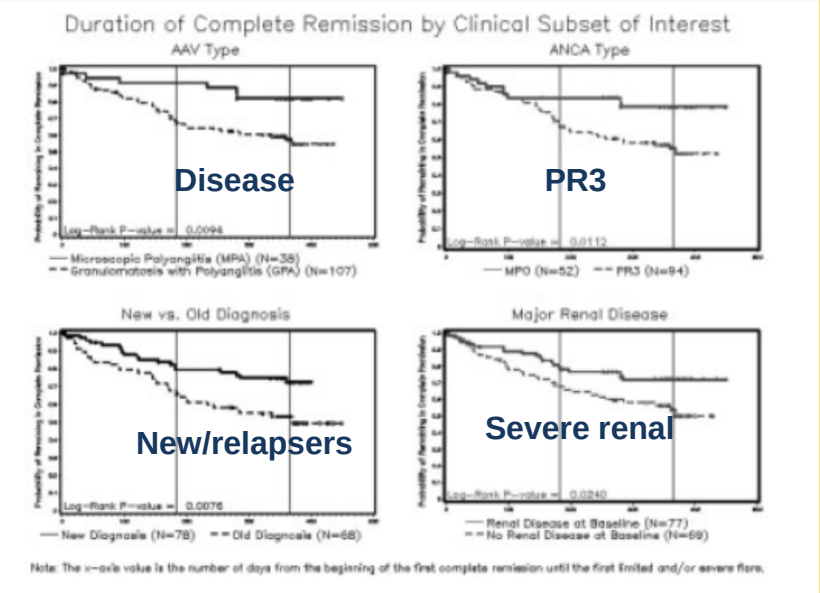
The initial treatment would be a once weekly infusion dosed at 375 mg/m^2 x 4 weeks.

The physician must confirm that the treatment would not be a maintenance infusion as maintenance infusions will not be funded.

Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient's last treatment cycle with Rituxan.

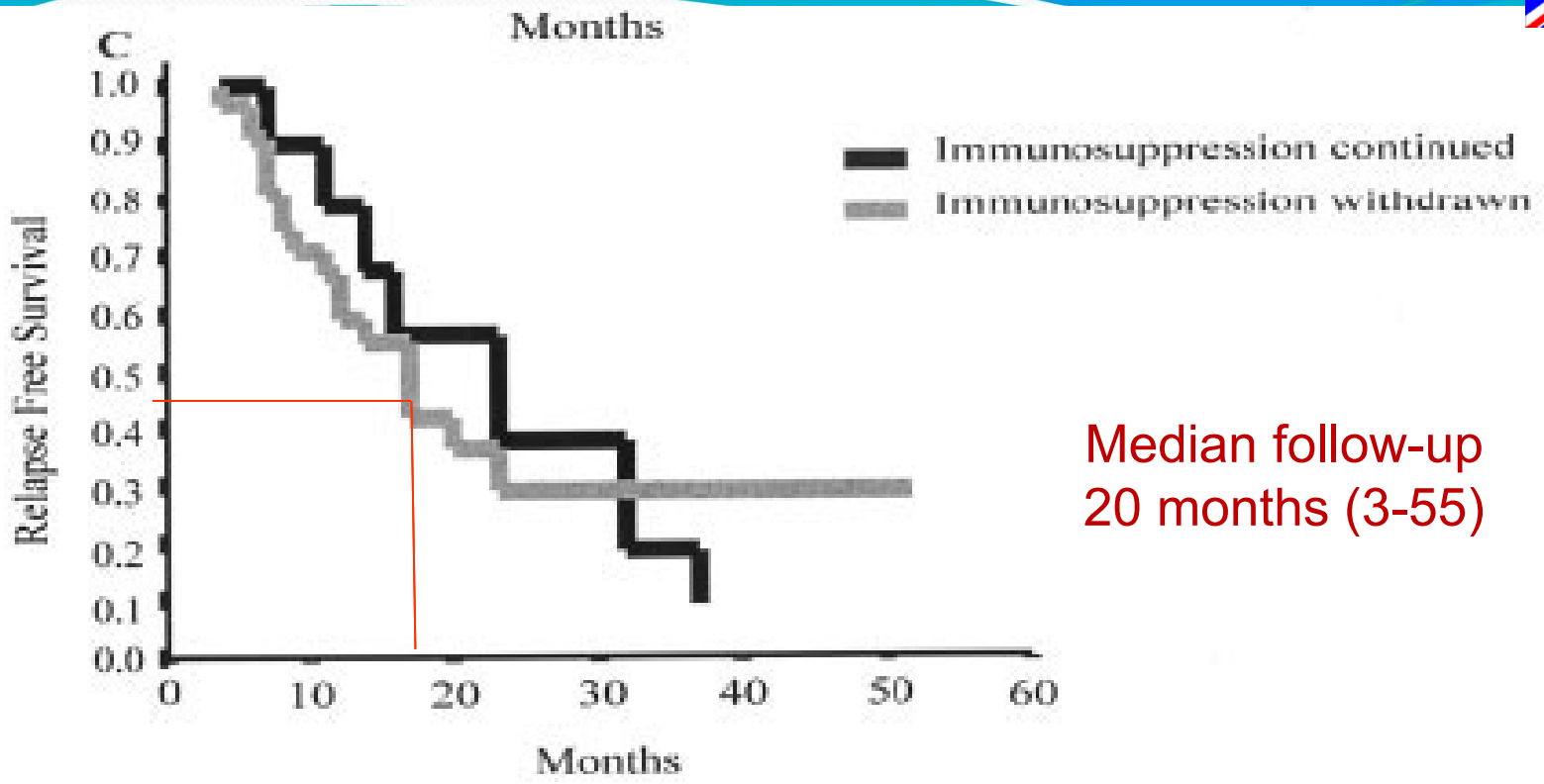
Extended RAVE follow-up

- 197 patients ANCA+ (49% new, 51% relapsers)
- CR (NS)
  - At M6: 64% RTX vs 53% CYC/AZA
  - At M12: 47% RTX vs 39% CYC/AZA
  - At M18: 39% RTX vs 33% CYC/AZA
- Higher risk of relapse
  - Relapsers
  - No renal disease
  - PR3+
  - GPA



- Flares occured only after B cell reconstitution in RTX arm

Stone JH et al. #2432 OP



Median follow-up
20 months (3-55)

IS stopped in (62%) when RTX started
(within the 6 (32) to 12 (5) following months)

Relapse 57% at 11.5 mo

(whether IS stopped or not, whichever ANCA status or organ invovement)

Jones R, Arthritis Rheum 2009;60:2156-68

RTX as maintenance

- 28 patients (4 MPA and 24 GPA)
- 4 [2−10] rituximab infusions, with a follow-up of 38 [21−97] months since last flare.

Roubaud-Baudron et al. J Rheumatol 2011

INDUCTION TREATMENT	TOTAL, N=28
RTX (375 mg/m²/wk x 4), n	**21**
Reason for RTX use	
CYC-CS failure	7
CYC-CS contra-indication	10
Dialysis	1
Young age	2
Other	1
CYC (0,6 g/m² D1, D14, D28 then /3wk), n	**5**
IVIg (2 g/Kg/mo), n	**2**
CUMULATIVE CYC DOSE, median [range], g	**48 [5-250]**

RTX Maintenance Treatment

Number of infusions, median [range]	4 [2–10]
Regimen, n	Total, n=28
375 mg/m² biannually	13
1 g biannually	4
1 g annually	3
Others	8
Indications	
After RTX induction treatment	21
Side effects	2
Azathioprine hepatitis	1
Mycophenolate mofetil GI intolerance	1
Persistent disease after 4 years on	2
Azathioprine	1
Mycophenolate mofetil	1
Previous relapses under azathioprine	2
Renal failure	1

RTX as maintenance

- 28 patients (4 MPA and 24 GPA)
- 4 [2−10] rituximab infusions
- follow-up 38 [21−97] months since last flare

- Two pulmonary relapses despite biannual rituximab infusions for both **= 7%**

Roubaud-Baudron et al. J Rheumatol 2011

Re-treatment n=38

- 6 pre-emptively
- 5 because of grumbling/RP

- 27 because of relapse:

→ 84% entered RC again with new RTX cycle
at M1.5 mo (mean)

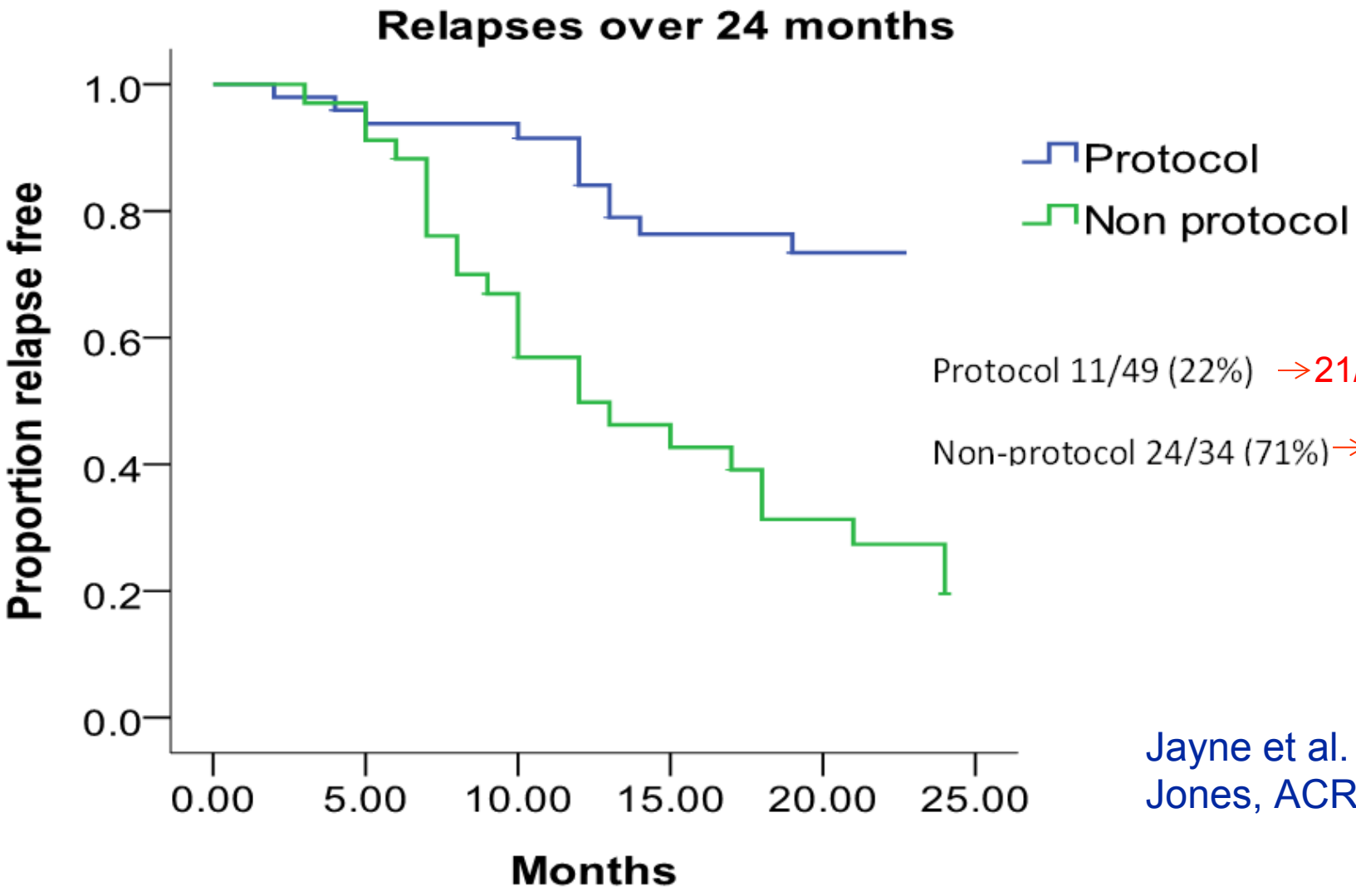
→ 1 patient with 7 cycles

→ **15 patients received 1 g / 6 mo = NO relapse (follow-up of 11 mo** – max. 3 infusions)

Jones R, Arthritis Rheum 2009;60:2156-68

Figure 1: Relapse free survival curves comparing protocolised and non-protocolised patients over 24 months

1g every 6 months for 2 years – other IS stopped

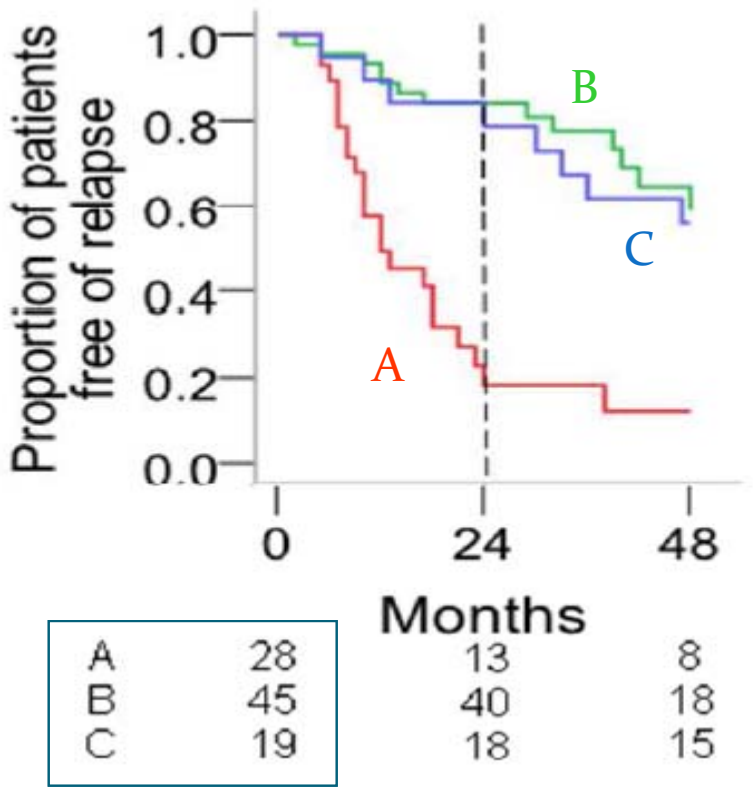


Protocol 11/49 (22%) →21/72 (22%)

Non-protocol 24/34 (71%)→26/34 (76%

Jayne et al.
Jones, ACR 2010

73 patients (61 GPA-12 MPA; 69 ANCA+; renal 12%, lung 27%)



At 2 years, relapses

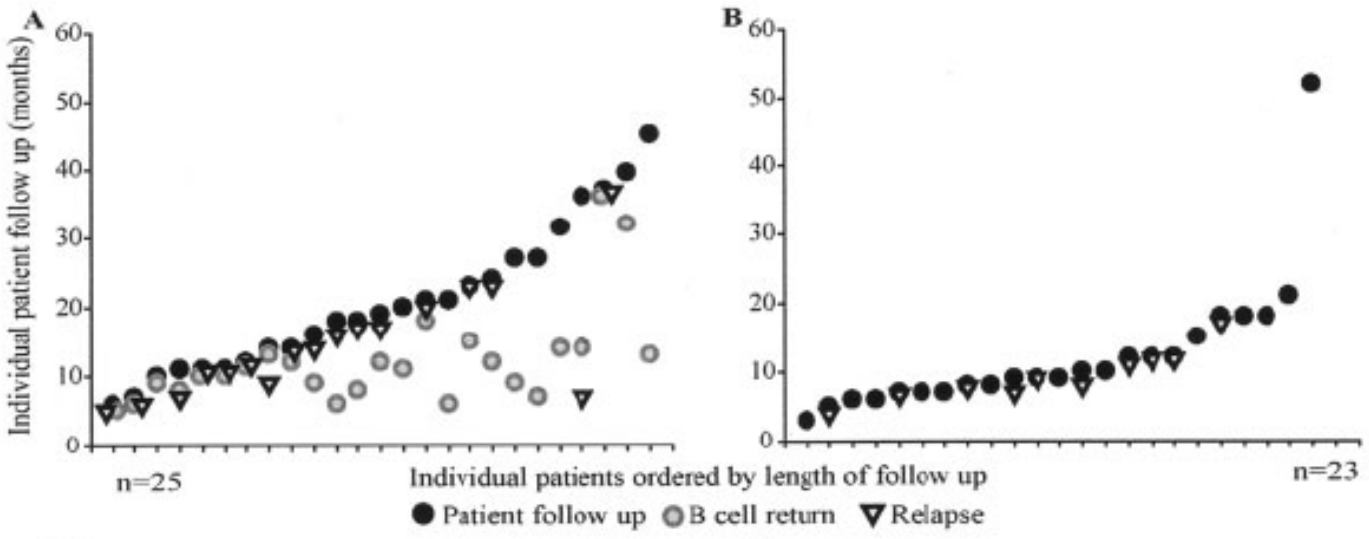
- 73% (19/26) Group A

  R. 12 (5-76) mo. after RTX induct.
- 12% (5/43) Group B (p<0.001)
- 11% (2/18) Group C (p<0.001)

At last follow-up, median 44 mo.

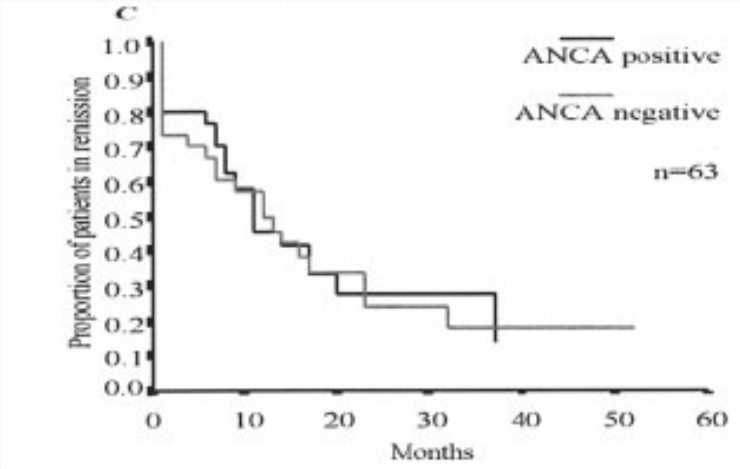
- 85% (22/26) Group A
- 26% (11/43) Group B (p<0.001)
- 56% (10/18) Group C (p=0.001)

Smith RM, Jones RB,. Arthritis Rheum. 2012 Jun 21



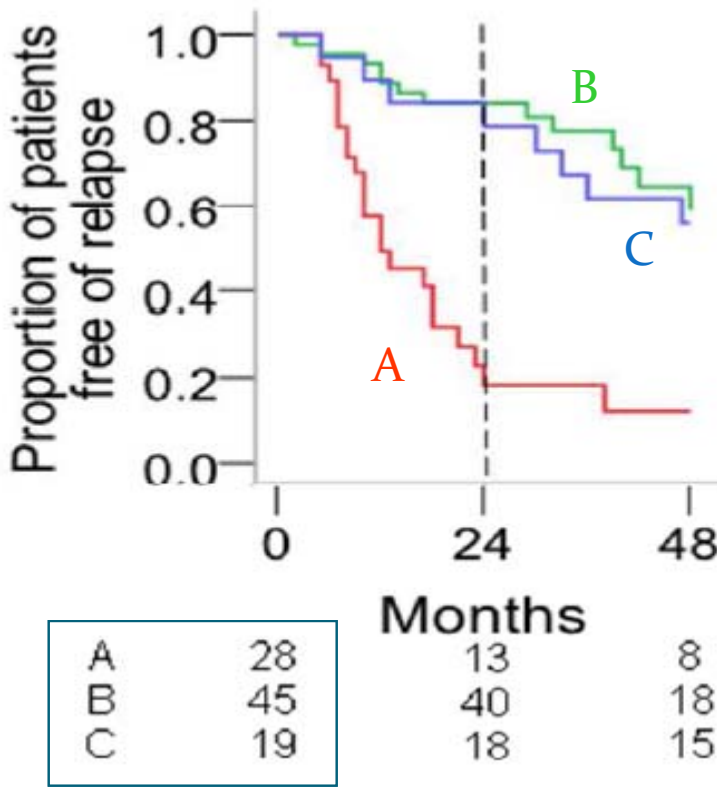
B reconstitution preceded relapse in 52%

32% of the patients with B reconstitution relapsed



Relapse not predicted by ANCA or CD19

Jones R, Arthritis Rheum 2009;60:2156-68



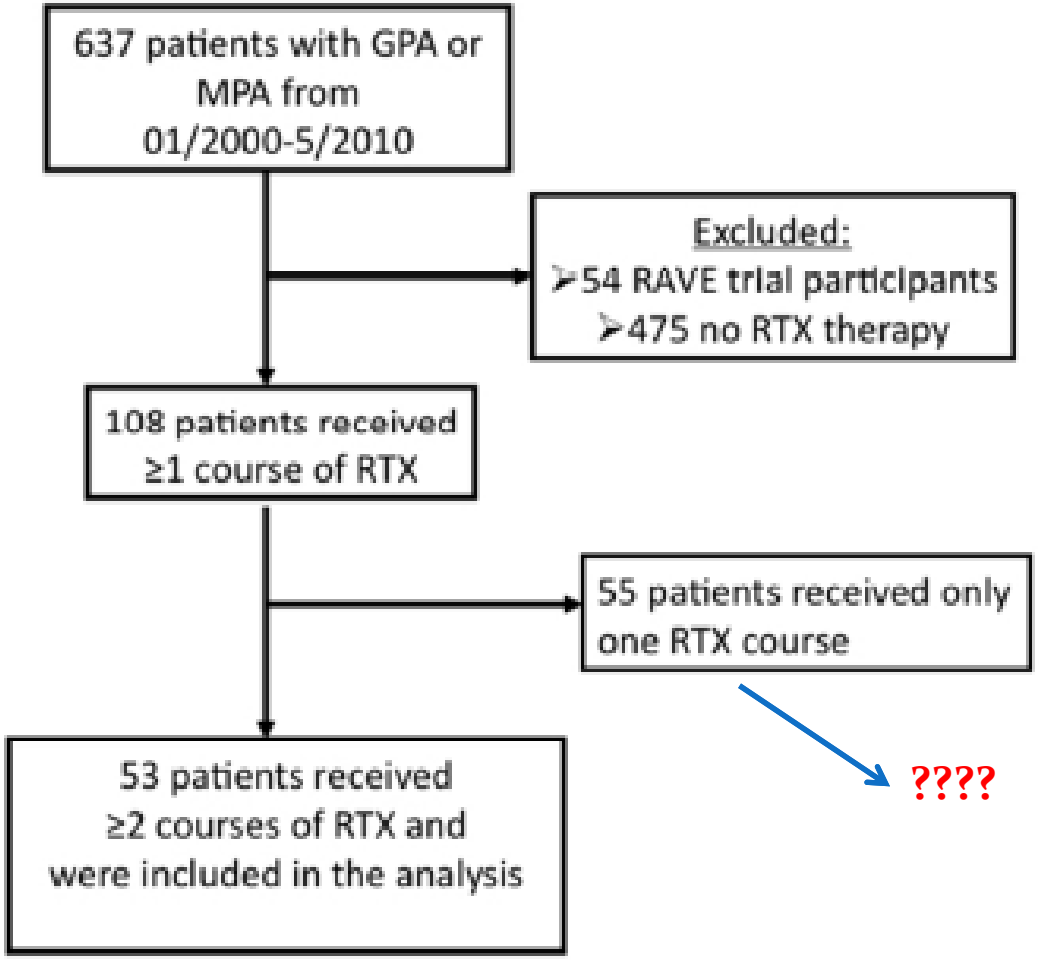
N=73

- Median time to B cell return
  - 11 months (2-30) in Group A
  - 7.5 months (1-32) in Group B (and C)
- At the time of first relapse
  - 12/18 (67%) in group A had detectable B cells
  - 4/10 (40%) in group B
  - 5/9 (56%) in group C
- At the time of relapse
  - 19/58 (33%) were ANCA+ by IIF and EIISA
  - 12/58 (21%) were persistently positive
  - 7/58 (12%) switched from ANCA negative to positive
  - ANCA status at relapse did not differ between groups
  - ANCA negativity in 67%

Smith RM, Jones RB,. Arthritis Rheum. 2012 Jun 21

Historical MAYO cohort study 01/2000-05/2010

- ≥2 RTX courses (375mg/m2x4 or 1gx2)



Rodrigo Cartin-Ceba, ***Arthritis & Rheumatism*** *Jun 07, 2012*

Historical MAYO cohort study 01/2000-05/2010

- ≥2 RTX courses (375mg/m2x4 or 1gx2)
- GPA (MPA), 52 antiPR3+, 1 ANCA negative
- renal 42%, lung 49%

- **53 patients** received 233 courses
  - 85 (36%) for relapse (21 patients)
  - 148 (64%) pre-emptively / biological ANCA rise and/or CD19 reconstitution (32 patients)

- Time to reconstitution = 8.5 months (same for 375mg vs 1g)
- All relapses preceded by B cell reconstitution and ANCA rise
- Remission maintained in all pre-emptively treated patients

Rodrigo Cartin-Ceba, ***Arthritis & Rheumatism*** *Jun 07, 2012*

- in the absence of better biomarkers routine re-treatment is the only strategy likely to be effective. Should improved biomarkers become available, closer adjustment of drug dosing to need will be achievable.

Smith RM, Jones RB,. Arthritis Rheum. 2012 Jun 21

- flares were not observed in the absence of peripheral blood B lymphocytes. [...] Timing of retreatment can be individualized based on serial B lymphocyte and PR3-ANCA determinations in these patients. Our result provide important information for trials conducted to determine the optimal timing and dosing of preemptive retreatments with RTX.

Rodrigo Cartin-Ceba, ***Arthritis & Rheumatism*** *Jun 07, 2012*

Ig level in RAVE trial

- 56/197 (28.4%) had low Ig levels (any isotype) at baseline (36 (64%) relapsers)
- Similar decrease in IgG, then M, A during Rx in both arms (among the 124 who completed M18 – 61/63)
- At 6 and 18 months, more patients had low Ig levels of all isotypes
  - IgG 18.2→65.1→44.9% CYC
    21.3→55.8→31.7% RTX
  - IgM 16.2→59→39.1% RTX
  - IgA 5.1→30.1→27.5%
- **Not correlated with the frequency of infections** (mainly URTI)
  - 1.86 infection per p. per year (N IgG level) versus 1.23 (low at any time) in RTX patients
  - 1.16 infection per p. per year (N IgG level) versus 1.38 (Low at any time) in CYC arm

Specks et al. (RAVE) #789

Adverse events

- None experienced a RTX-infusion−related adverse event
- 15 had hypogammaglobulinemia (predominantly IgM)
- 3 had infectious events (1 cutaneous abscess, 1 otitis and 1 fatal H1N1 flu).

Roubaud-Baudron et al. J Rheumatol 2011

Severe adverse events

- Severe infections
  - 6/28 (21%) patients A
  - 12/45 (27%) patients B
  - 5/19 (26%) patients C (NS)
  - 4 died (1A, 3B – 2 unknown, 1 abdo sepsis, A chest sepsis)
- 18-26% had hypogammaglobulinemia at the time of first RTX
- 33-44% in groups B and C at 2 years (not monitored in patients A)

Smith RM, Jones RB,. Arthritis Rheum. 2012 Jun 21

Adverse events

- 16 infusion-related events (14 during 1st infusion)
- 30 infections: mostly URTI
- 2 died: Pneumocystosis 2 months after stopping CTX; acute myeloid leukemia (41g of CYC)

- Decrease in all Ig but measured in few patients

Rodrigo Cartin-Ceba, ***Arthritis & Rheumatism*** *Jun 07, 2012*

- We did not routinely prescribe antibiotic, antiviral or fungal prophylaxis and no unusual infection trends were identified. However,…

Smith RM, Jones RB,. Arthritis Rheum. 2012 Jun 21
Hugle et al, Arthritis Care Res (Hoboken). 2010 Nov;62(11):1661-4

- Repeated and prolonged B lymphocyte depletion seems to be associated with a low risk of infections, but PCP prophylaxis for the duration of B lymphocyte depletion is justified.

Rodrigo Cartin-Ceba, ***Arthritis & Rheumatism*** *Jun 07, 2012*

MAINRITSAN

MAINtenance of remission using RITuximab in Systemic ANCA-associated vasculitides

1st inclusion in October 2008, last in June 2010

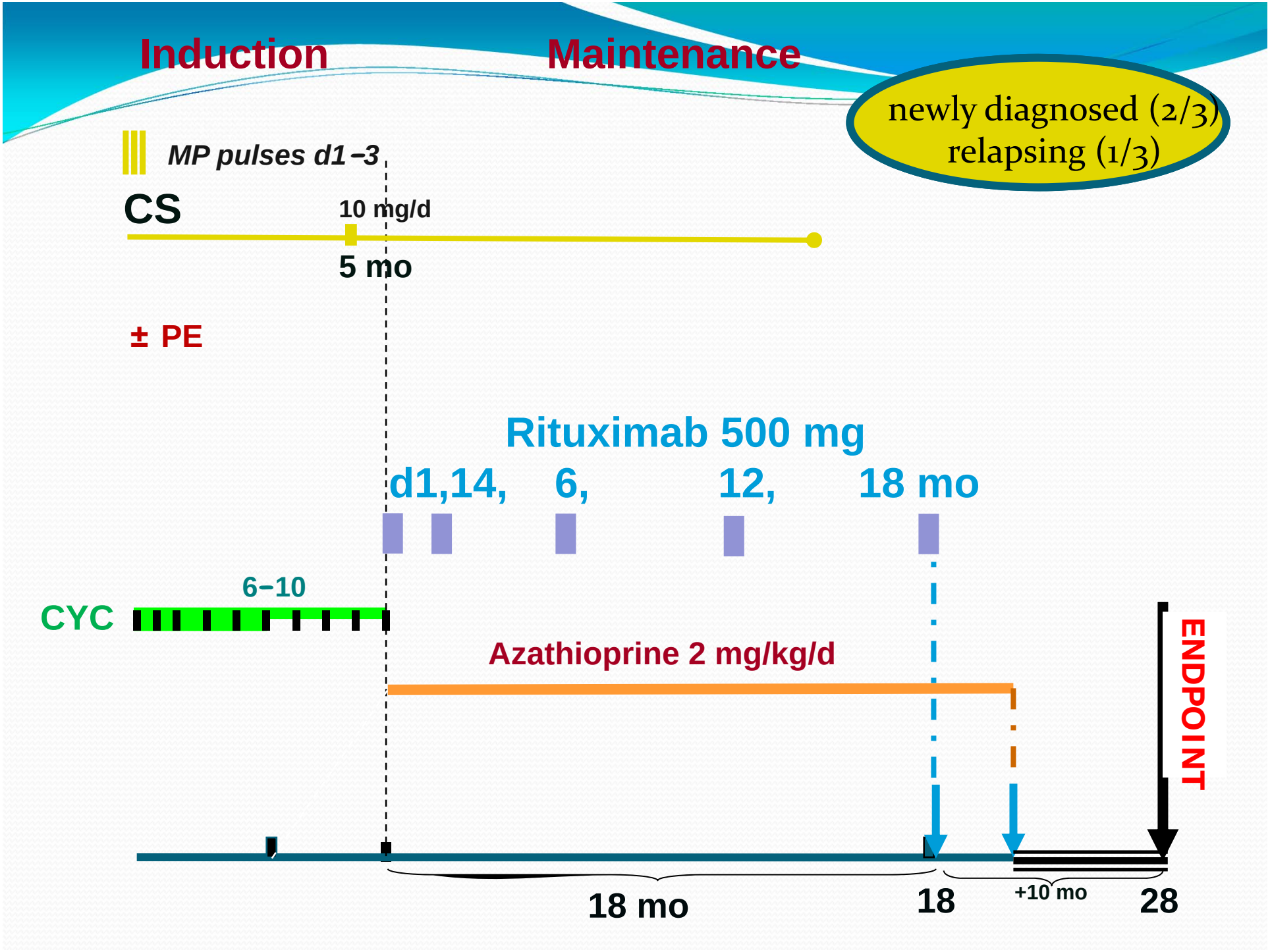
Systemic GPA or MPA (with FFS ≥ 1), 18–75 year-old

Newly diagnosed (2/3) or relapsers (1/3)

AFTER achieving remission with CS–CYC

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

French Vasculitis Study Group


Induction
Maintenance
newly diagnosed (2/3)
relapsing (1/3)
MP pulses d1–3
CS
10 mg/d
5 mo
± PE
Rituximab 500 mg
d1,14, 6, 12, 18 mo
6–10
CYC
Azathioprine 2 mg/kg/d
ENDPOINT
18 mo
18
+10 mo
28

MAINRITSAN

Statistical hypothesis:

> 25% absolute reduction of the relapse rate

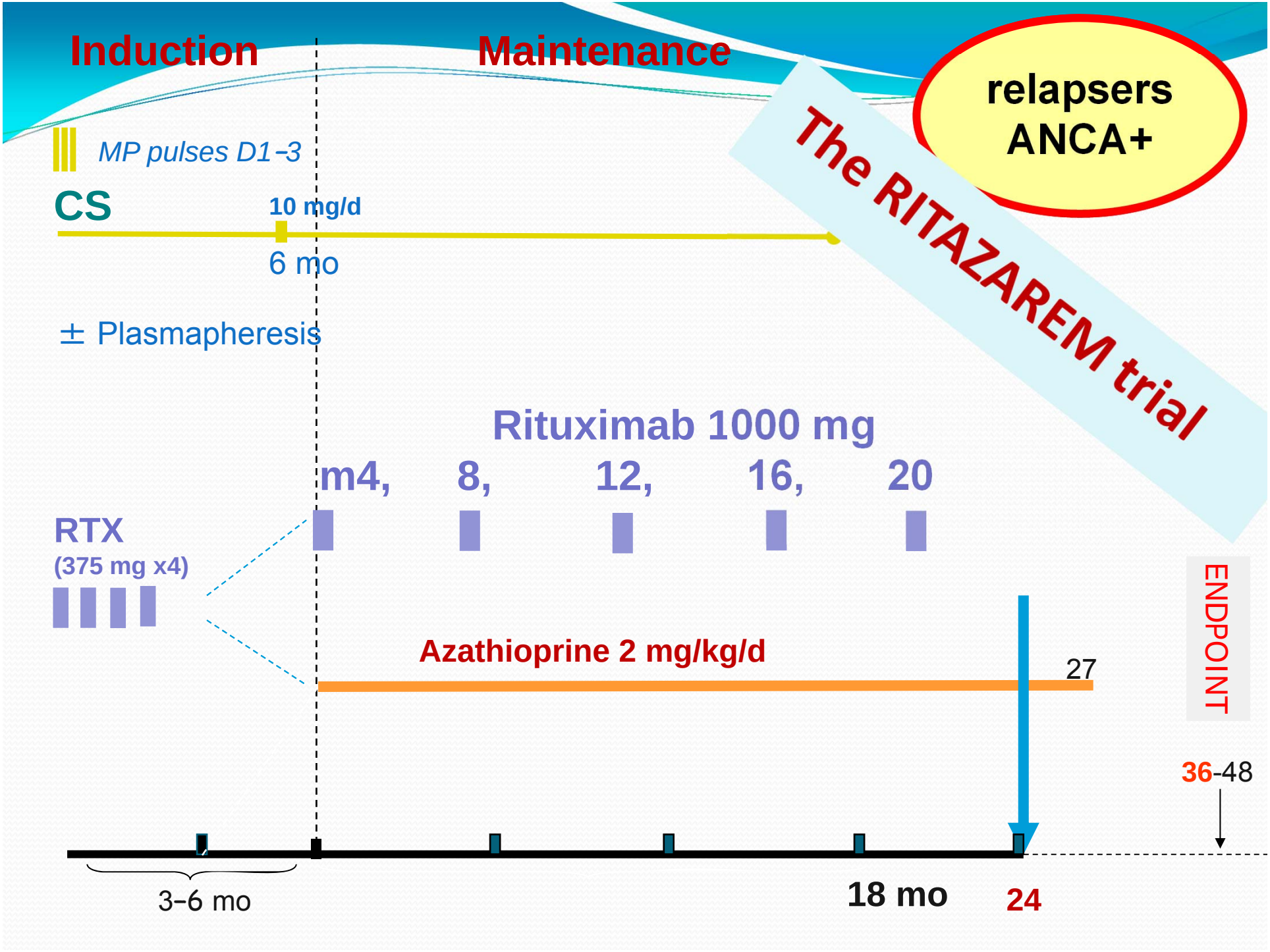
with RTX at M28 of maintenance

40% with AZA (WEGENT) → 15% with RTX

P = 80%; alpha = 5%; bilateral test

→ 118 patients enrolled

RESULTS = ACR 2012* (if accepted)


Induction
Maintenance
relapsers
ANCA+
The RITAZAREM trial
MP pulses D1–3
CS
10 mg/d
6 mo
± Plasmapheresis
Rituximab 1000 mg
m4,
8,
12,
16,
20
RTX
(375 mg x4)
Azathioprine 2 mg/kg/d
27
ENDPOINT
36-48
3–6 mo
18 mo
24

REIMBURSEMENT CRITERIA

For the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.
2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.
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a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
b) The patient has failed three months of oral cyclophosphamide therapy; OR
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Renewals will be considered provided that, the patient meets the same criteria for initial approval and the request for retreatment is made no less than 6 months after the last does of the patient's last treatment cycle with Rituxan.

Welcome Ritazarem!

+ induction for 1st relapsers
+ maintenance (for relapsers)

2nd annual CanVasc meeting

Montréal, QC

November 22nd, 2012

Registration and information on

http://www.canvasc.ca

April 14 - 17 2013

16th International Vasculitis & ANCA Workshop

"Institut des Cordeliers"
Paris - France

Scientific committee :

Pr. Loïc Guillevin
(president)

Organisation :

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