FACULTÉ DE MÉDECINE

CMR CENTRE MALADIES RARES
VASCULARITES | SCLÉRODERMIES
GOUGEROT-SJÖGREN | LUPUS

HÔPITAUX UNIVERSITAIRES PARIS CENTRE
Cochin • Port-Royal • Tarnier • Broca
La Collégiale • La Rochefoucauld • Hôtel-Dieu

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Benjamin Terrier

Department of Internal Medicine, Cochin Hospital

National Reference Center for Systemic Autoimmune Diseases

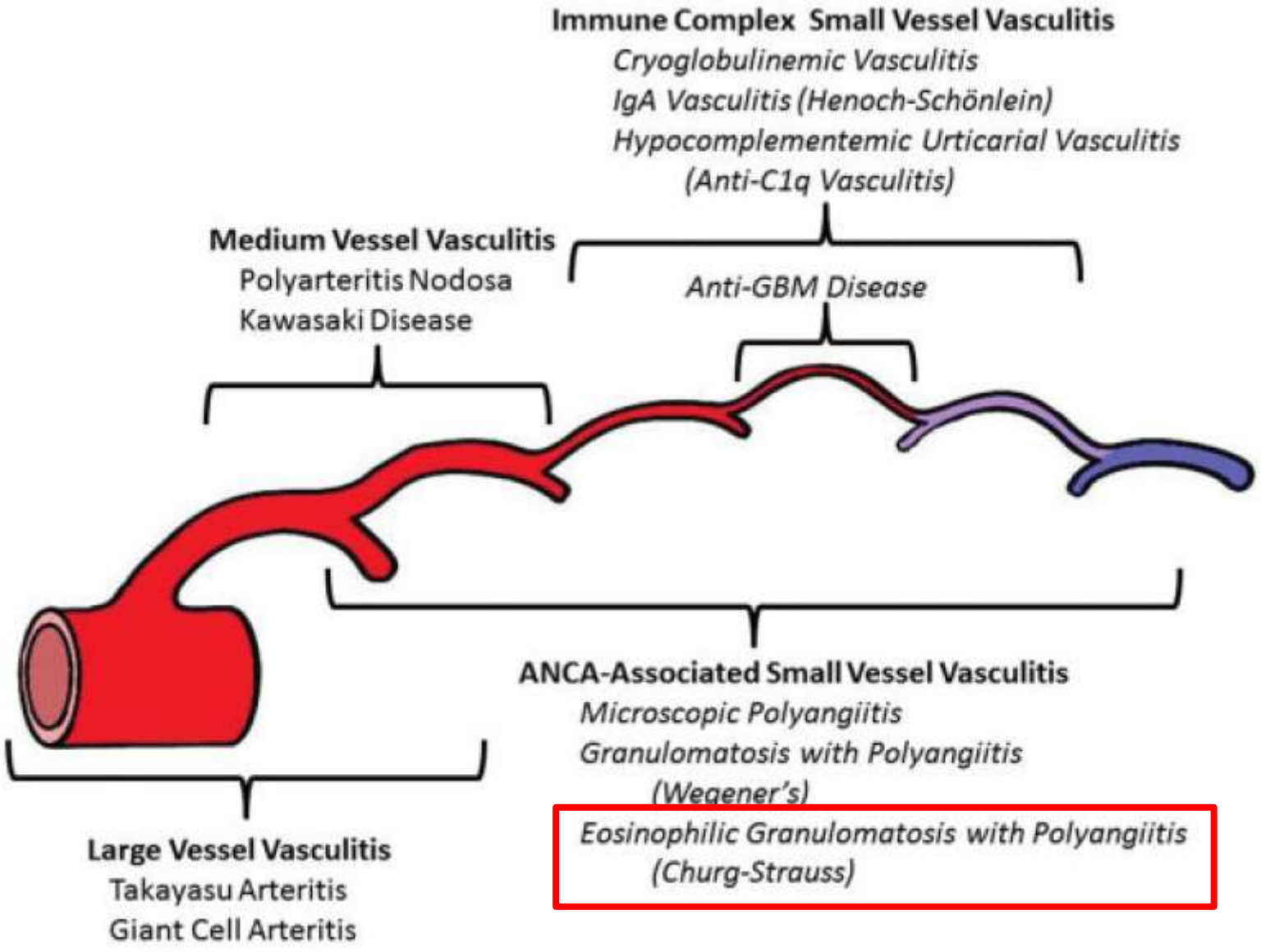
Paris Descartes University, Paris, France

FVSG FRENCH VASCULITIS STUDY GROUP

Conflict of interest

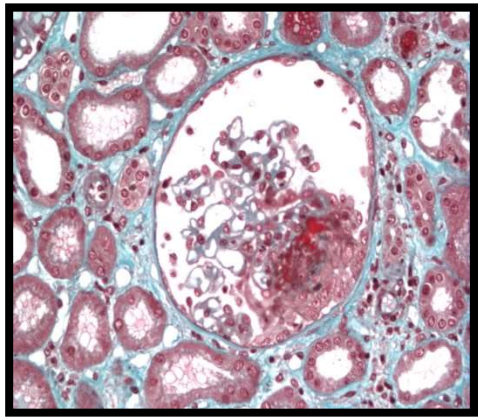
- **Advisory board : Roche, Chugaï, Vifor, LFB, Grifols, AstraZeneca**
- **Consulting fees : Roche, Chugaï, Vifor, LFB, Grifols, AstraZeneca**
- **Travel expenses : Roche, LFB, Grifols, GSK, Octapharma, Janssen**

Chapel Hill 2012 Consensus conference



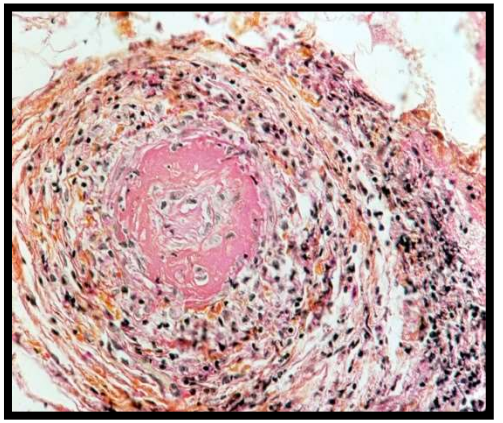
Jennette, Arthritis Rheum, 2013

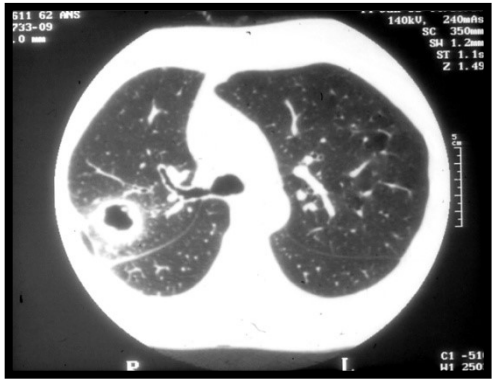
ANCA-associated vasculitides

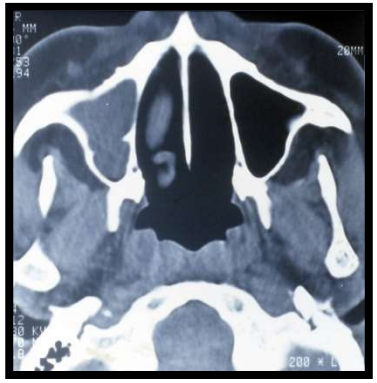


Small-vessel necrotizing vasculitis

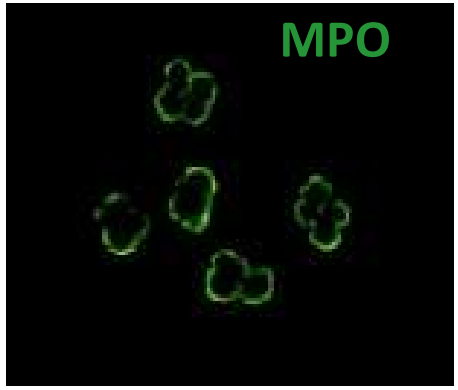
Systemic disease with pulmonary, ENT and renal involvement

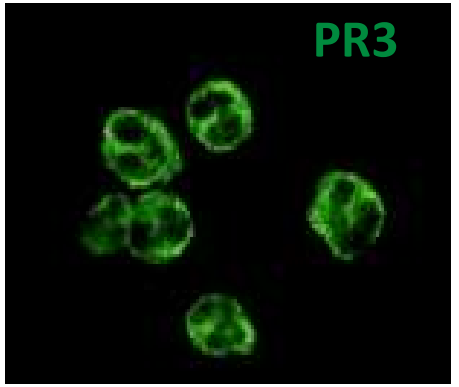






ANCA	MPO	PR3
GPA (Wegener)	10 %	85 %
MPA	60 %	30 %
EGPA (Churg)	30%	0 %

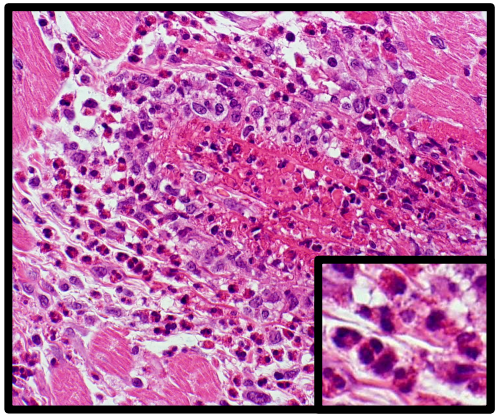




Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Described by Churg and Strauss in 1951

Eosinophil-rich and necrotizing granulomatous inflammation predominantly affecting small to medium vessels

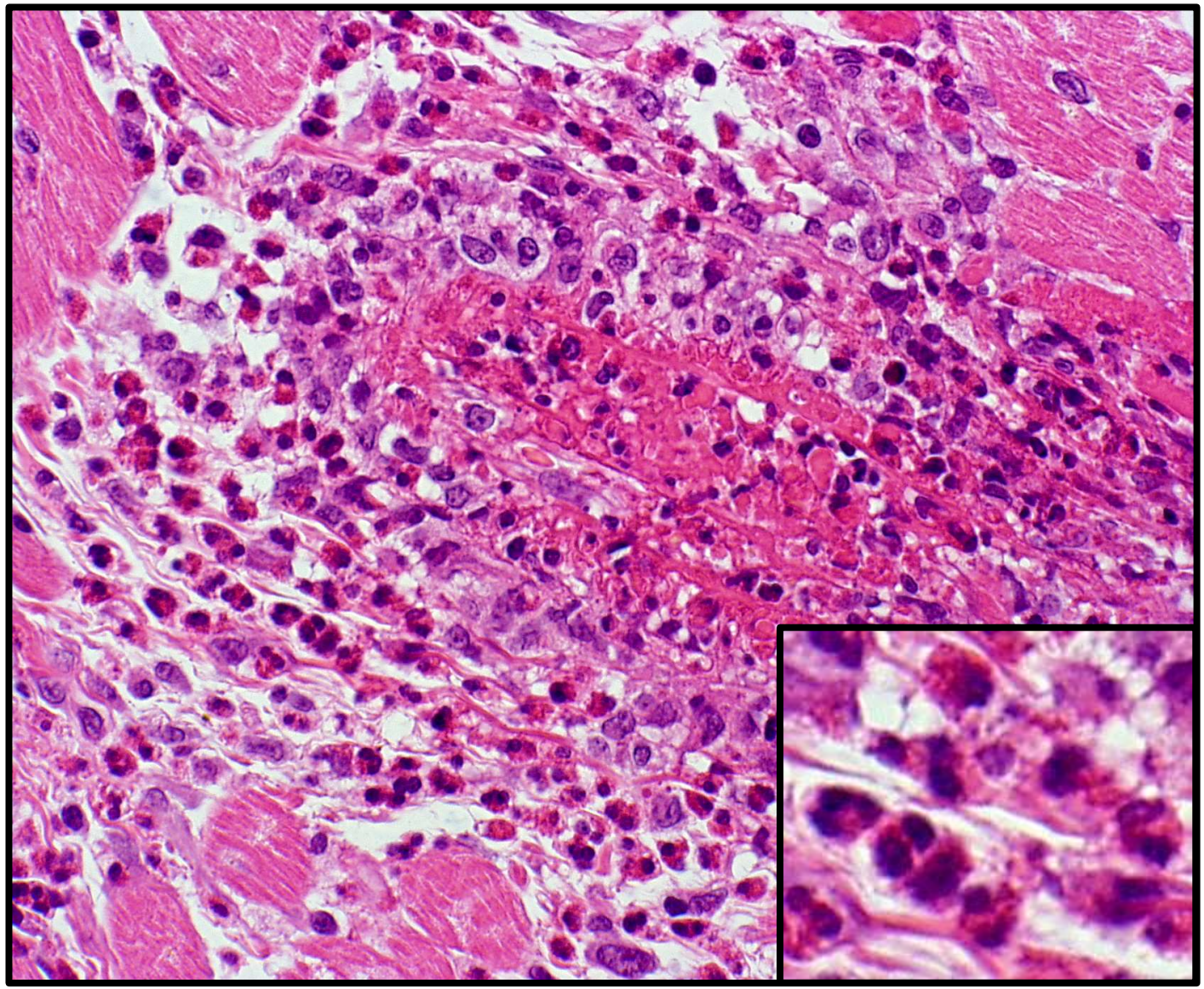


Hypereosinophilic asthma with vasculitis manifestations :

- **Peripheral neuropathy**
- **Cardiomyopathy**
- **Glomerulonephritis**
- **Purpura**
- **ANCA**

Jennette, Arthritis Rheum, 2013
Masi, Arthritis Rheum, 1990
Churg et Strauss, Am J Pathol, 1951

Eosinophil-rich necrotizing vasculitis



1990 ACR criteria

Criteria applicable in vasculitis patients

This definition includes the presence of at least 4 of the following:
• Eosinophil count >10% of peripheral blood leukocytes on more than one occasion off prednisone therapy (historical)
• Asthma
• Neuropathy (mono or poly)
• Pulmonary infiltrates
• Paranasal sinus abnormality
• Extravascular eosinophils

The presence of any 4 or more of the 6 criteria yields a sensitivity of 85% and a specificity of 99.7%

Masi, Arthritis Rheum, 1990

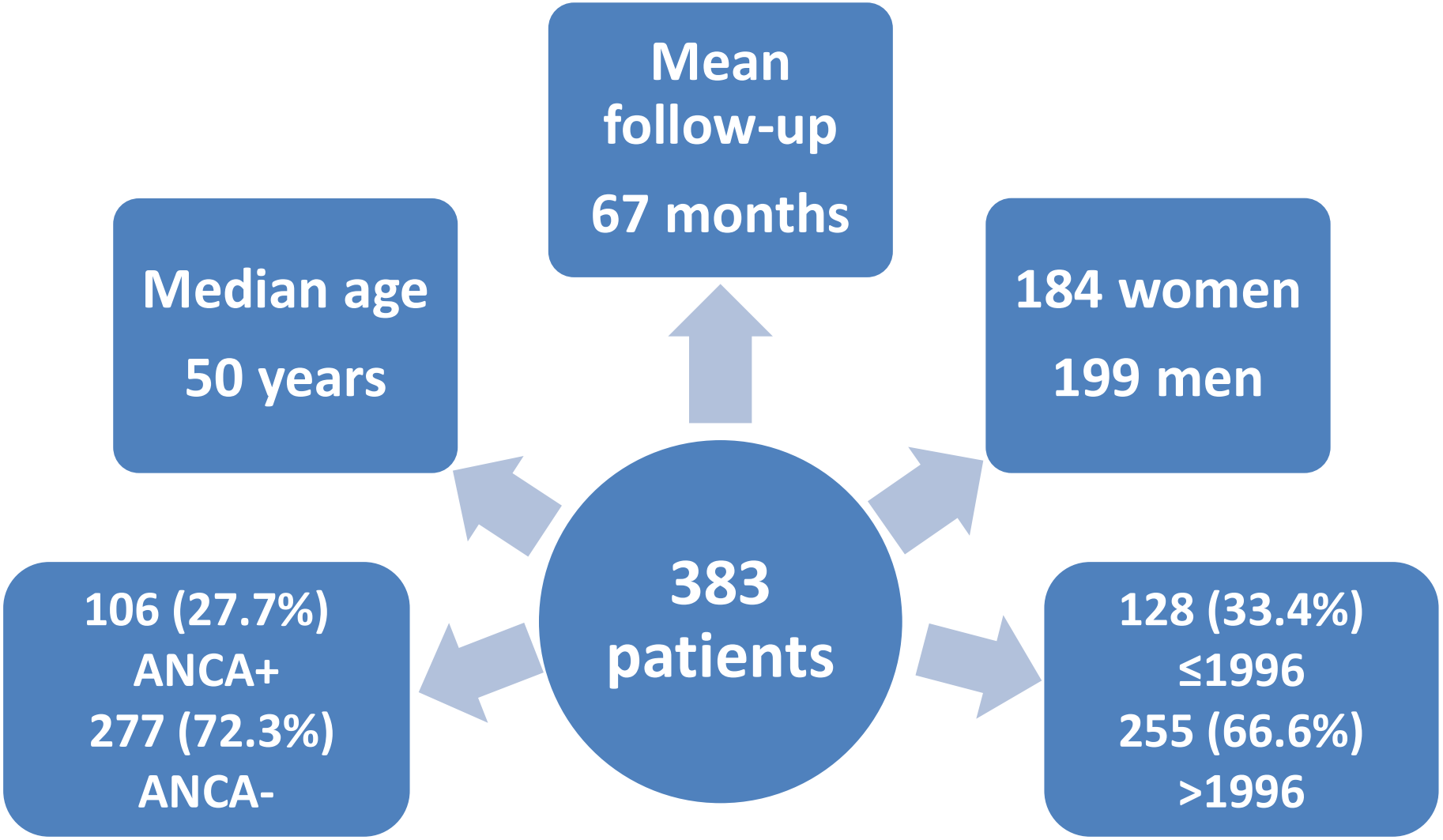
MIRRA trial inclusion criteria

Diagnosis of EGPA based on current or past evidence of asthma AND hypereosinophilia (>1.0x10^9/L and/or >10%), PLUS AT LEAST 2 of the following criteria :

- **Presence of an eosinophil-rich vasculitis, an eosinophilic perivascular infiltrate, or a granulomatous infiltrate with eosinophils**
- **Peripheral neuropathy (polyneuropathy, multiple mononeuropathy)**
- **Non fixed pulmonary infiltrates**
- **Sinonasal abnormalities**
- **Cardiomyopathy (echography and/or MRI)**
- **Glomerulonephritis**
- **Alveolar hemorrhage (BAL or CT)**
- **Vascular purpura**
- **Positive ANCA (MPO or PR3)**

Wechsler, N Engl J Med, 2017

FVSG retrospective study (1957-2009)



Comarmond, Arthritis Rheum, 2013

Clinical manifestations of EGPA

Clinical manifestations	n (%)
History of allergy	104 (27)
Asthma prior to EGPA diagnosis (yrs)	9.3 ± 10.8
Asthma	349 (91.1)
ENT	184 (48)
Lung infiltrates	89 (23.2)

Comarmond, Arthritis Rheum, 2013

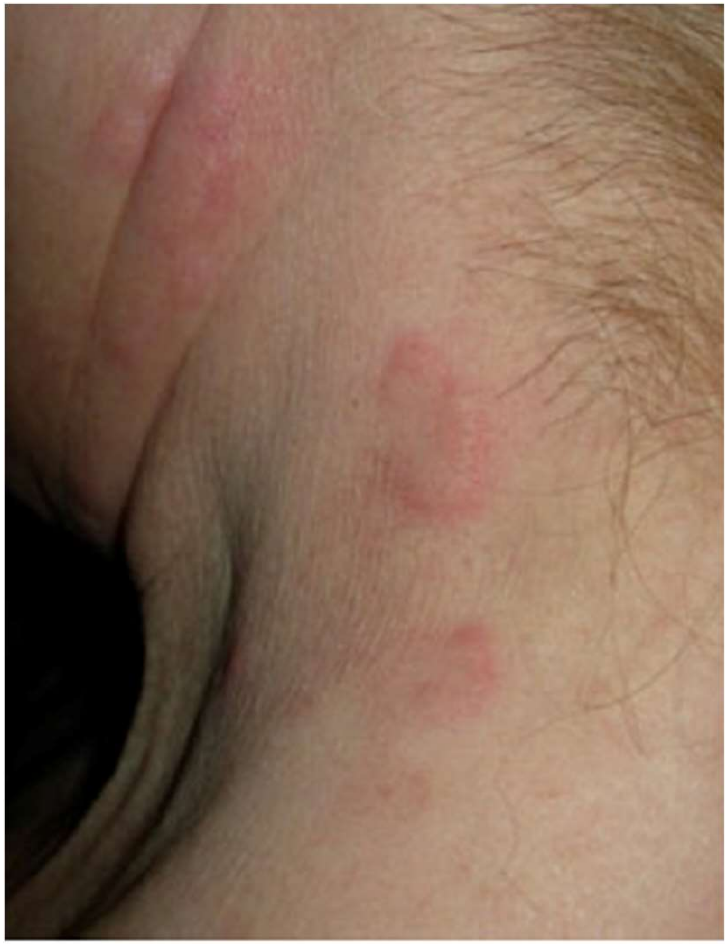
Clinical manifestations of EGPA

Reference	No. of patients	Mean age at diagnosis (y)	Asthma	ENT
Abu-Shakra, 1994 [8]	12	48	100	83
Lanham, 1984 [9]	16	38	100	70
Oh, 2006 [10]	17	37	100	–
Della Rossa, 2002 [11]	19	46	100	58
Haas, 2001 [12]	20	43	100	45
Gaskin, 1991 [13]†	21	47	100	–
Reid, 1998 [14]	23	57	96	52
Chumbley, 1977 [15]	30	47	100	70
Solans, 2001 [16]	32	43	100	Rhinitis 62
Keogh, 2003 [17]	91	49	99	74
Sinico, 2005 [18••]	93	52	96	77
Guillevin, 1999 [19]	96	48	100	Sinusitis 61
Sablé-Fourtassou, 2005 [20••]	112	52	100	77

Pagnoux, Curr Opin Rheumatol, 2007

Clinical manifestations of EGPA

	n (%)
Fever	149 (38.9)
Myalgias	149 (38.9)
Arthralgias	114 (29.8)
Peripheral neuropathy	197 (51.4)
Skin lesions	152 (39.7)



Comarmond, Arthritis Rheum, 2013

Clinical manifestations of EGPA

	n (%)
Cardiac manifestations	**105 (27.4)**
Renal *Proteinuria >0.4 g/24h* *Creatinine>140 µmol/L*	**83 (21.7)** *49 (12.8)* *11 (4.3)*

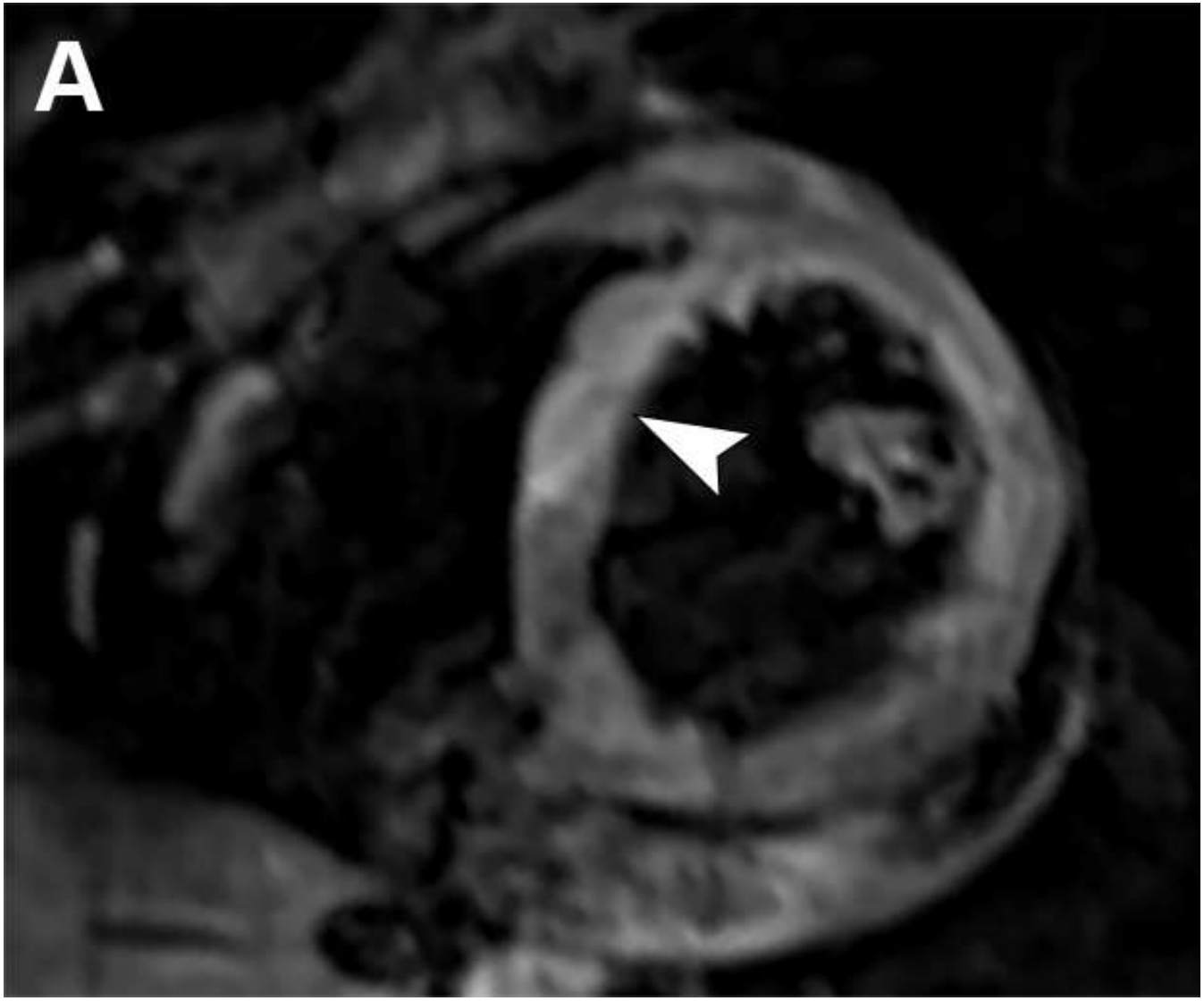
Comarmond, Arthritis Rheum, 2013

Clinical manifestations of EGPA

Reference	Skin	Heart	PNS	CNS	GI	Kidney
Abu-Shakra, 1994 [8]	67	42	92	8	8	8
Lanham, 1984 [9]	48	47	66	–	59	49
Oh, 2006 [10]	59	18	65	–	18	0
Della Rossa, 2002 [11]	63	31	58	–	47	21
Haas, 2001 [12]	75	50	65	–	50	35
Gaskin, 1991 [13]†	50	15	70	–	58	80†
Reid, 1998 [14]	Urticaria 26, purpura 26	Cardiac failure 17, pericarditis 26	70	39	Pain 17, bleeding 9	57
Chumbley, 1977 [15]	67	16	63	–	17	20
Solans, 2001 [16]	81	Myocarditis 25, pericarditis 12	72	6	44	13
Keogh, 2003 [17]	57	Myocarditis 13, pericarditis 8	76	11	31	25
Sinico, 2005 [18••]	53	16	65	14	22	27
Guillevin, 1999 [19]	51	30	78	8.3	33	26
Sablé-Fourtassou, 2005 [20••]	52	Myocarditis 14, pericarditis 35 35 Myocarditis 24, pericarditis 25	72	9	32	16

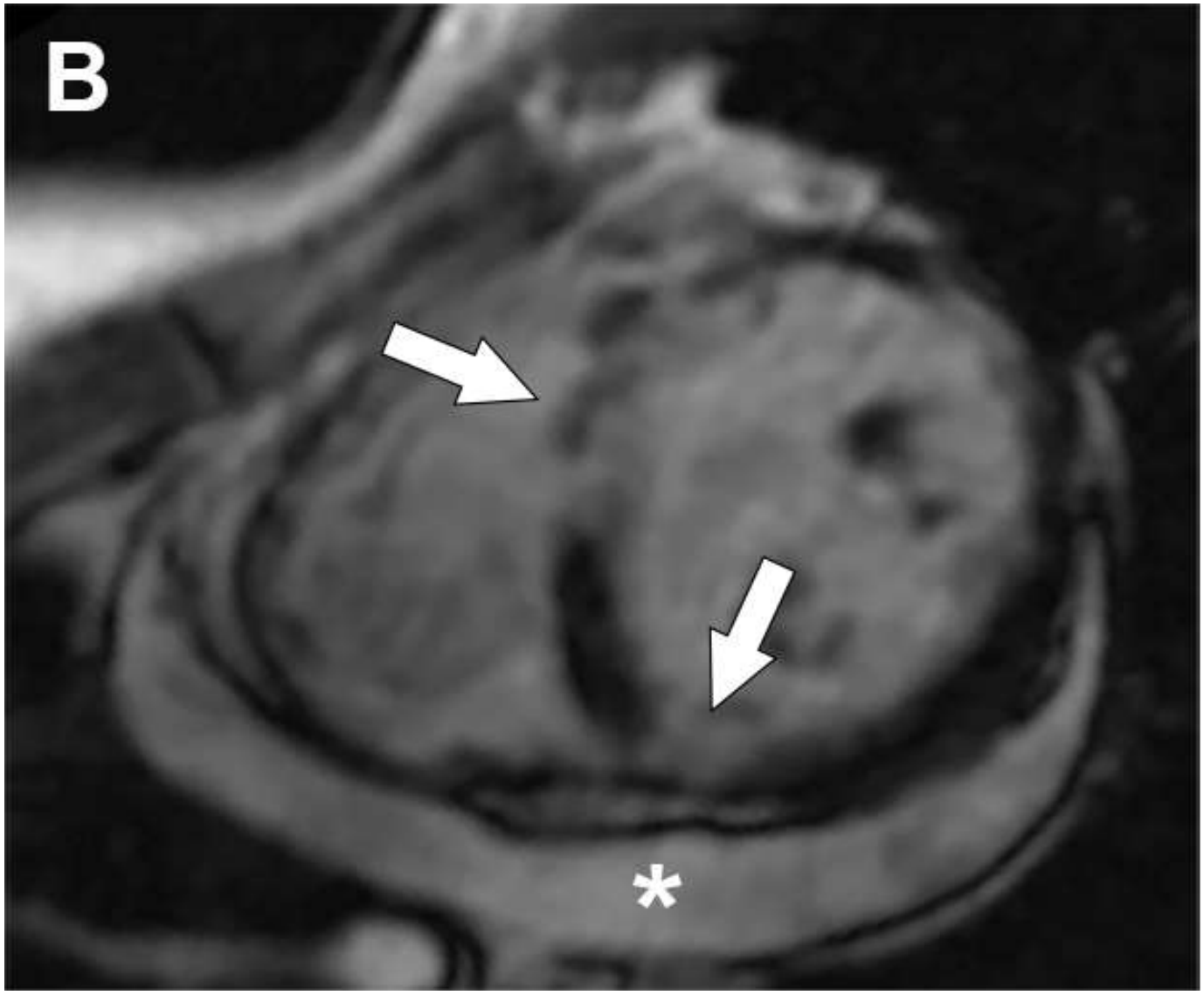
Pagnoux, Curr Opin Rheumatol, 2007

Cardiac manifestations - Myocarditis



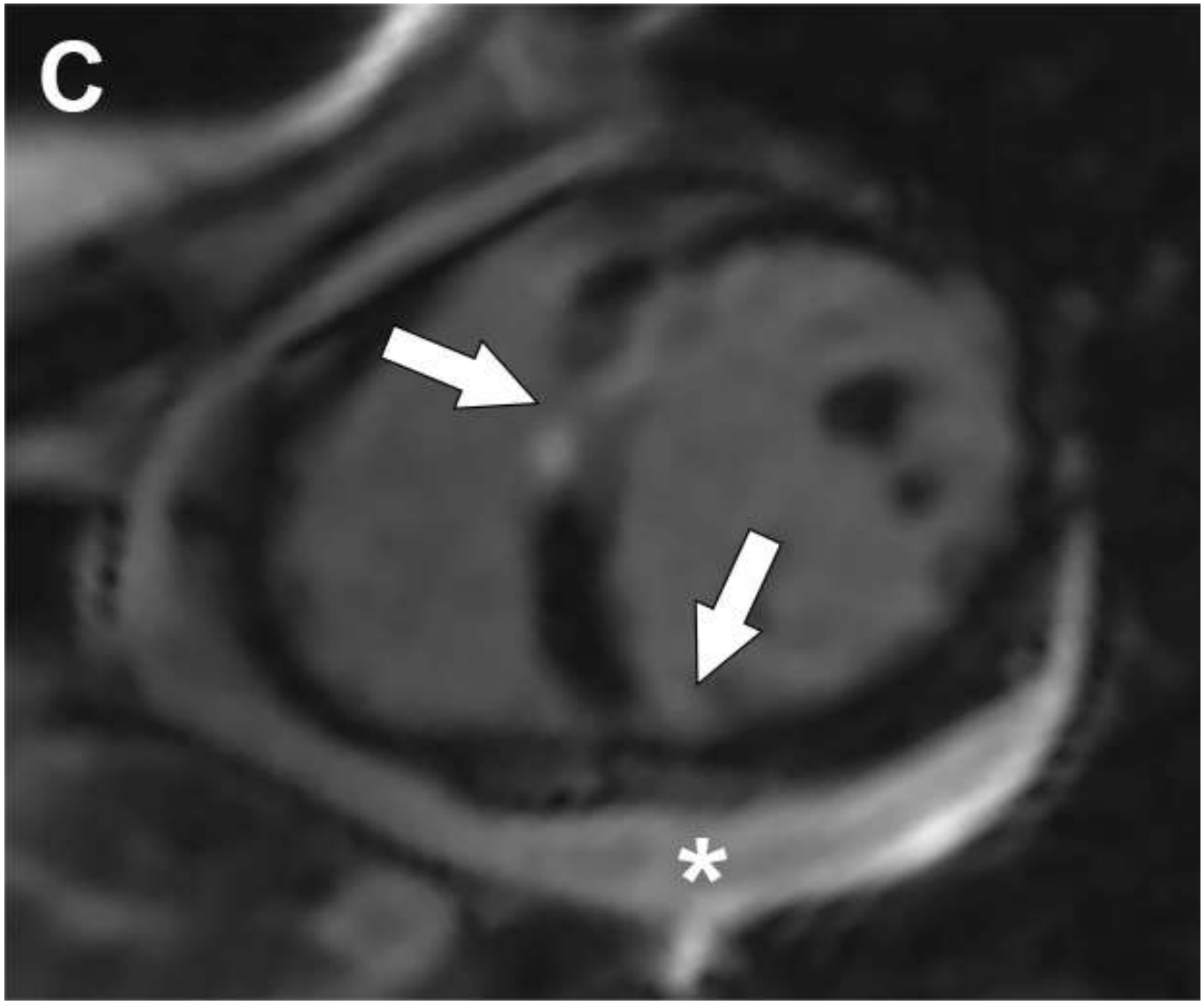
Myocardial edema on T2-weighted sequences

Cardiac manifestations - Myocarditis



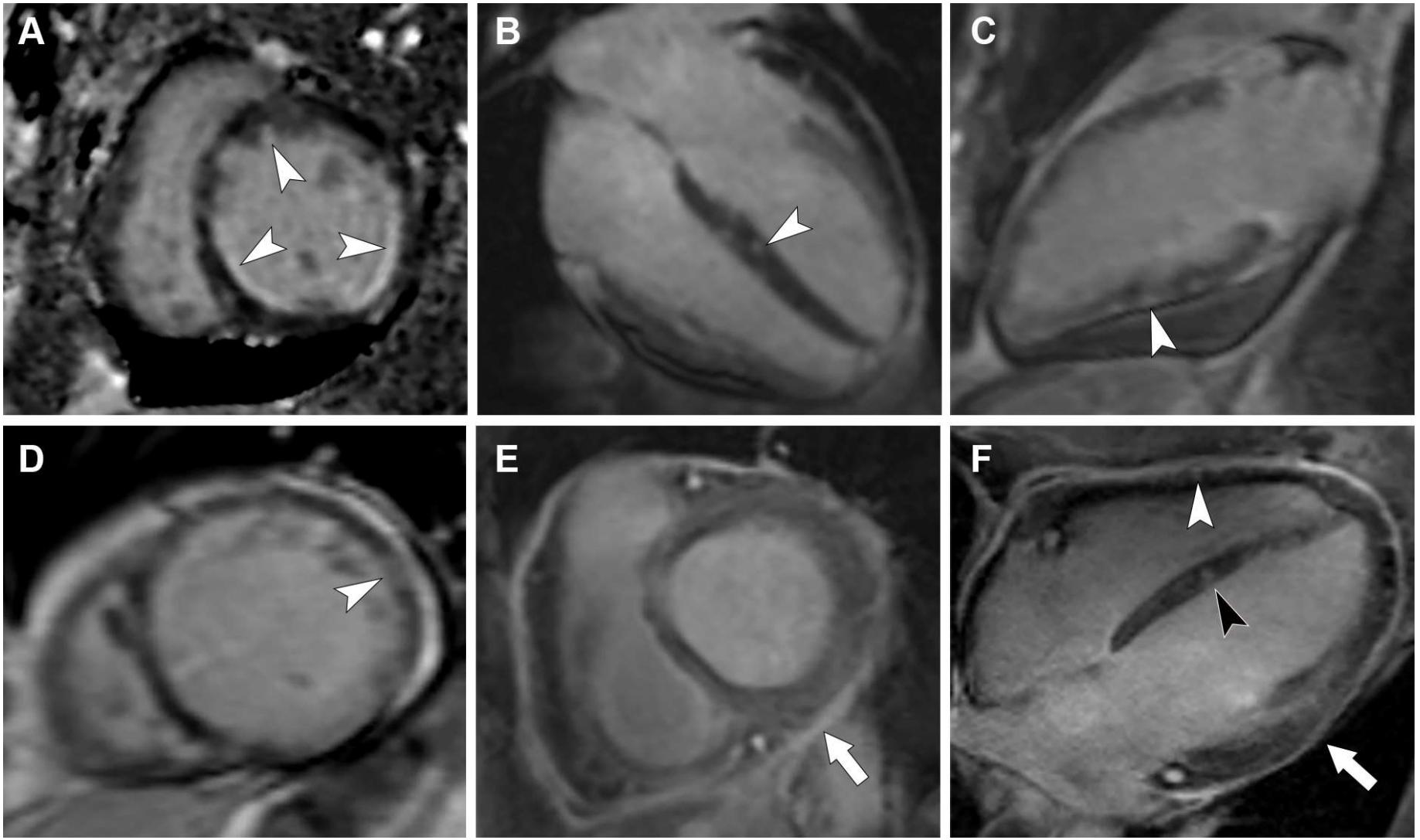
Early gadolinium enhancement on T1-weighted sequences

Cardiac manifestations - Myocarditis



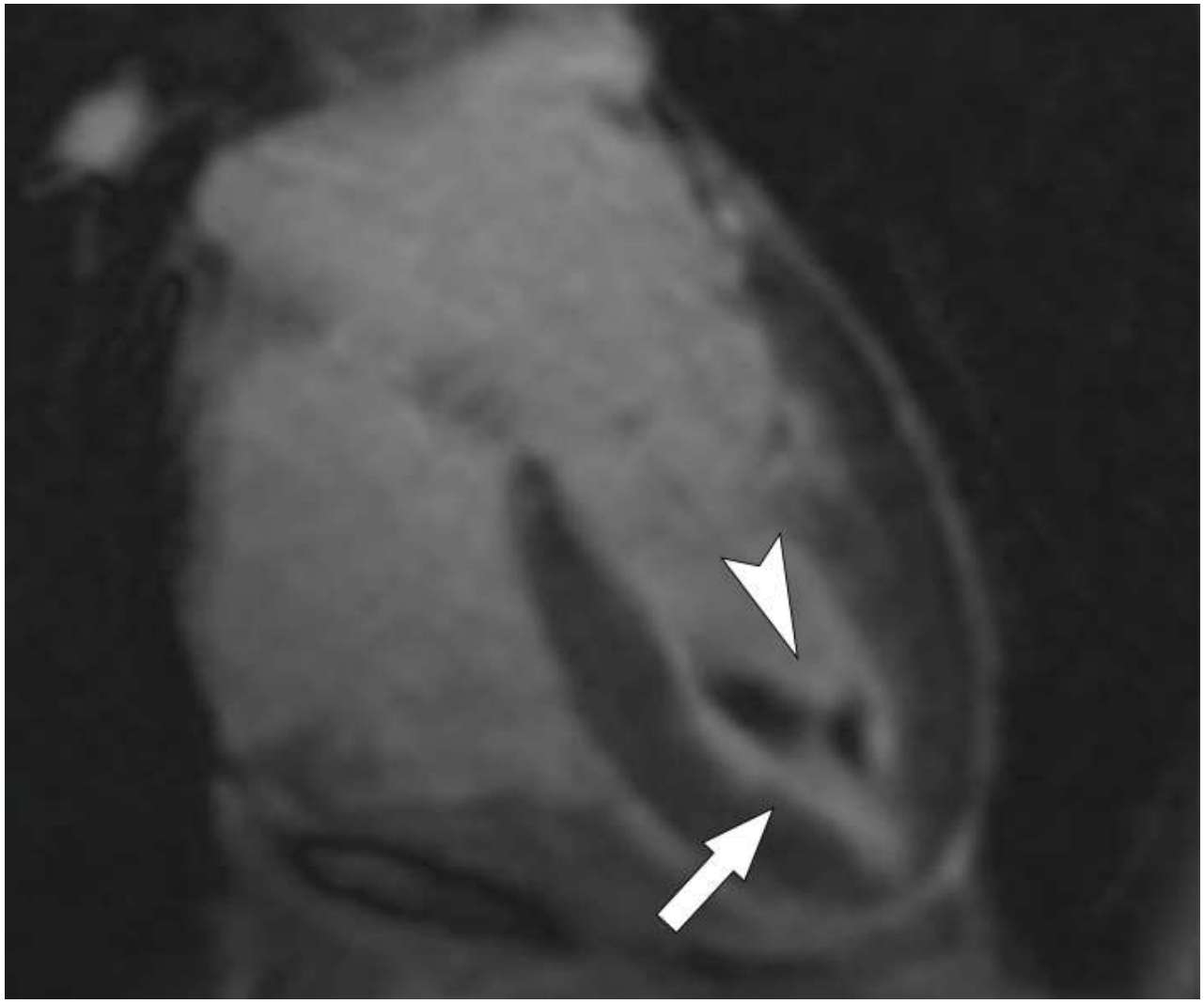
Late gadolinium enhancement on T1-weighted sequences

Cardiac manifestations - Myocarditis



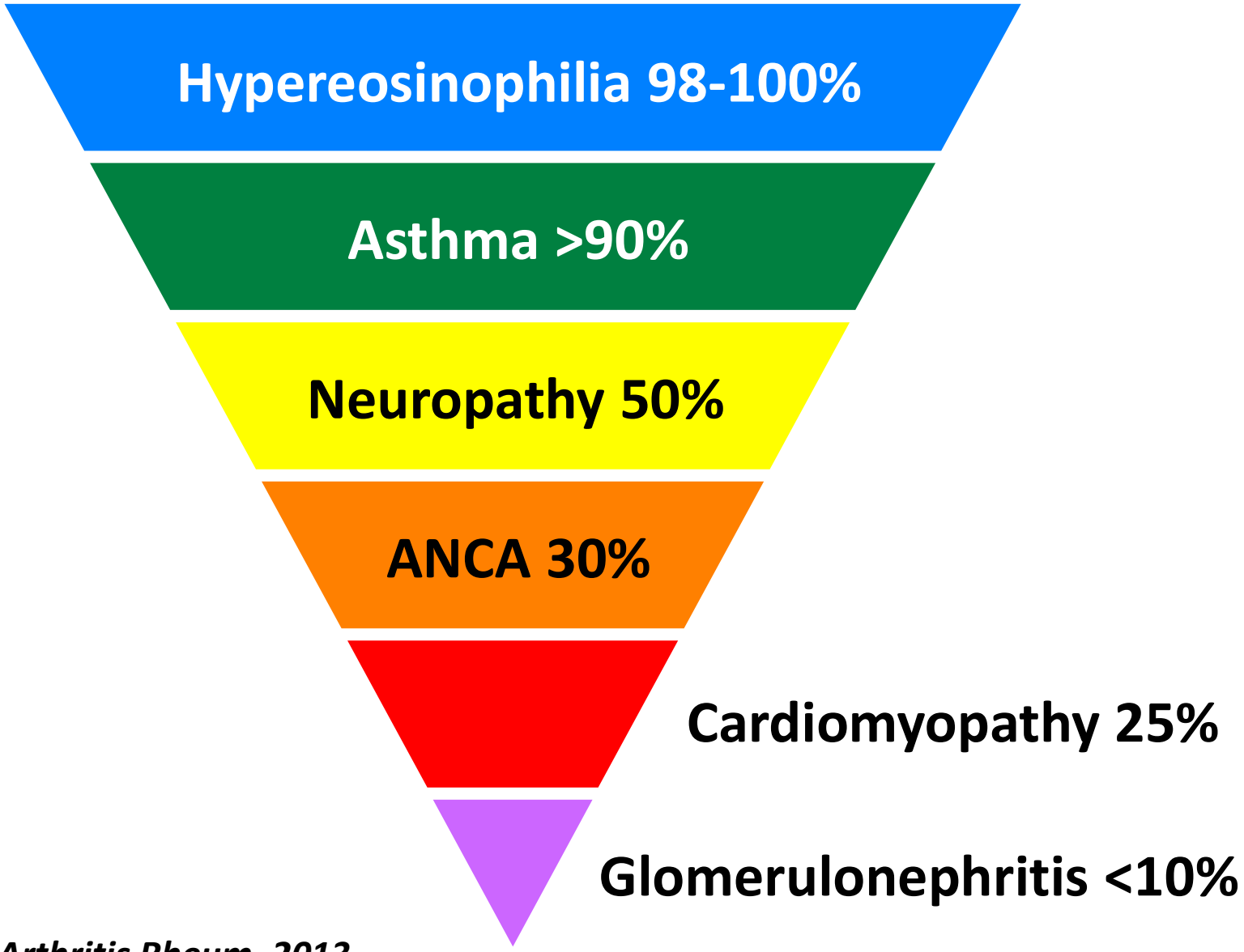
Different patterns of late gadolinium enhancement

Cardiac manifestations - Myocarditis



Endomyocardial fibrosis - Subendocardial LGE (arrow) and apical thrombus (arrowhead)

Clinical and biological manifestations



Comarmond, Arthritis Rheum, 2013

Disease phenotypes according to ANCA

Sinico, Arthritis Rheum, 2005	***Sablé-Fourtassou, Ann Intern Med, 2005***
ANCA+	**ANCA+**
Renal involvement	Renal involvement
Multiple mononeuropathy	Multiple mononeuropathy
Purpura	Vasculitis on biopsy
Alveolar hemorrhage	
ANCA-	**ANCA-**
Heart involvement	Heart involvement
Lung involvement	Fever

Disease phenotypes according to ANCA

Clinical manifestations	ANCA +	ANCA –	*P*
Asthma	92.5	90.6	0.57
Peripheral neuropathy	**63.2**	**46.9**	**0.04**
ENT	**60.4**	**43.3**	**0.01**
Cutaneous	46.2	37.2	0.11
Pulmonary infiltrates	40.6	37.9	0.63

Comarmond, Arthritis Rheum, 2013

Disease phenotypes according to ANCA

Clinical manifestations	ANCA +	ANCA –	*P*
Heart	**17.9**	**31.1**	**0.01**
Gastrointestinal tract	22.6	23.5	0.86
Kidney	27.4	19.5	0.10
Proteinuria >0.4 g/24h	**22.6**	**9**	**<0.01**
Hematuria	**22.6**	**7.6**	**<0.01**
Creatinin >140 µmol/L	6.3	3.4	0.31

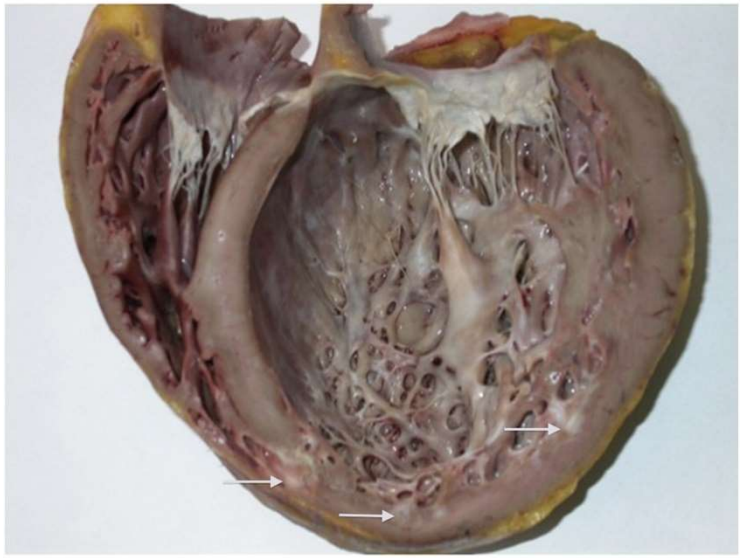
Comarmond, Arthritis Rheum, 2013

The absence of ANCA is not synonymous of the absence of vasculitis

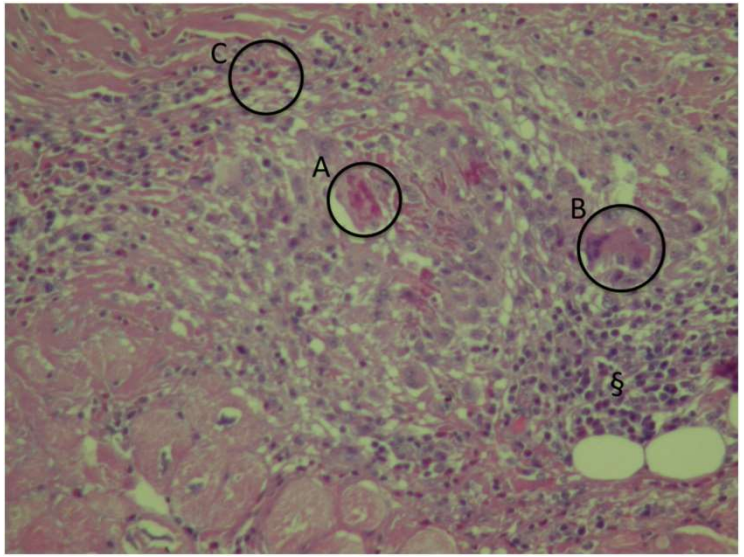
Data from 9 ANCA- patients with EGPA and heart involvement

Despite ongoing immunosuppression, histologic examination of 7/8 patients' explanted hearts showed histologic patterns suggestive of active vasculitis

A



B



Groh, J Heart Lung Transplant, 2014

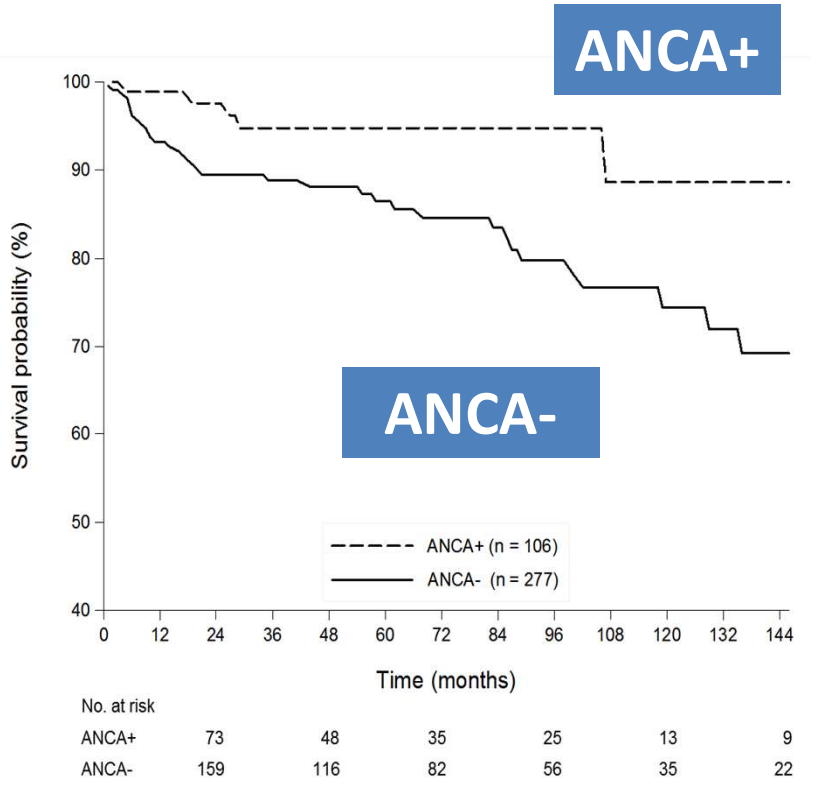
Outcome according to ANCA status

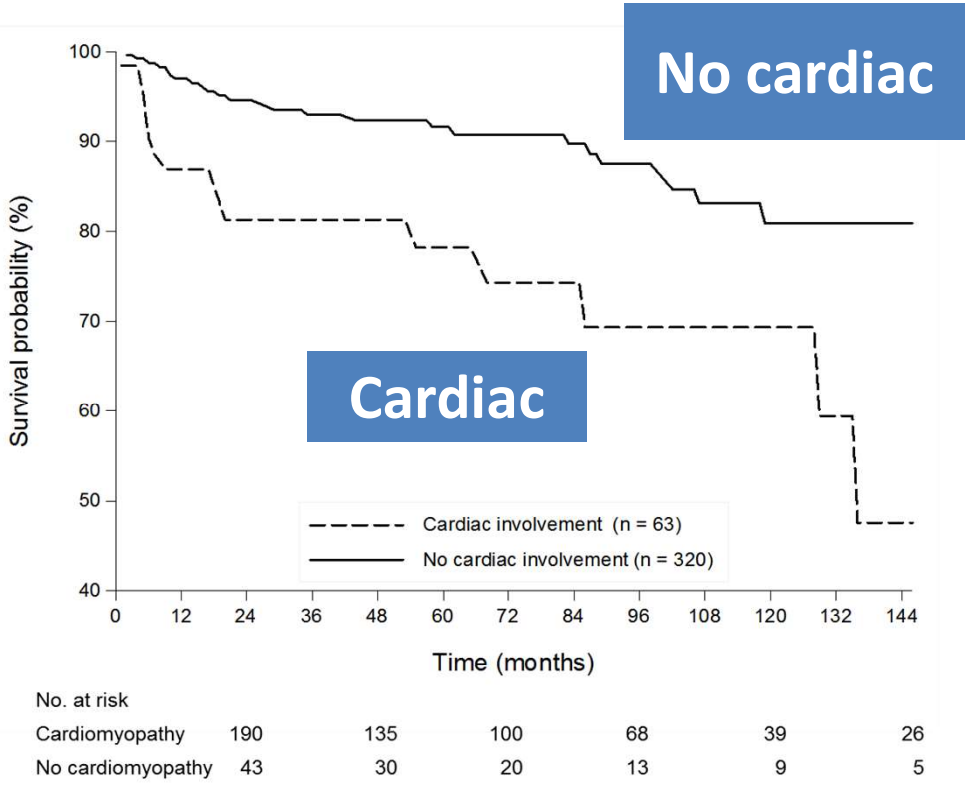
Follow-up	All	ANCA+	ANCA-	*P*
Death (%)	11.8	5.7	14.1	0.02
Relapse (%)	25.3	35.9	21.3	<0.01

Predictive factors of relapse	HR	95% CI
Eosinophil count	0.99	0.99–0.99
ANCA+	1.84	1.19–2.82

Comarmond, Arthritis Rheum, 2013

EGPA prognosis : Long-term survival





	ANCA +	ANCA -	*P*
At 5 yr	94.8%	86.5%	0.05
95% CI	86.6–98.0	80.5–90.7	

	No cardiac	Cardiac	*P*
At 5 yr	91.6%	78.2%	<0.02
95% CI	86.7–94.8	64.3–87.3	

Comarmond, Arthritis Rheum, 2013

EGPA prognosis : risk factors for death

	HR	95% CI
Cardiomyopathy	4.22	2.17–8.20
Age at diagnosis	1.06	1.03–1.09
Diagnosis <1996	3.20	1.53–6.70

<u>Causes of death</u>

Cardiomyopathy +++

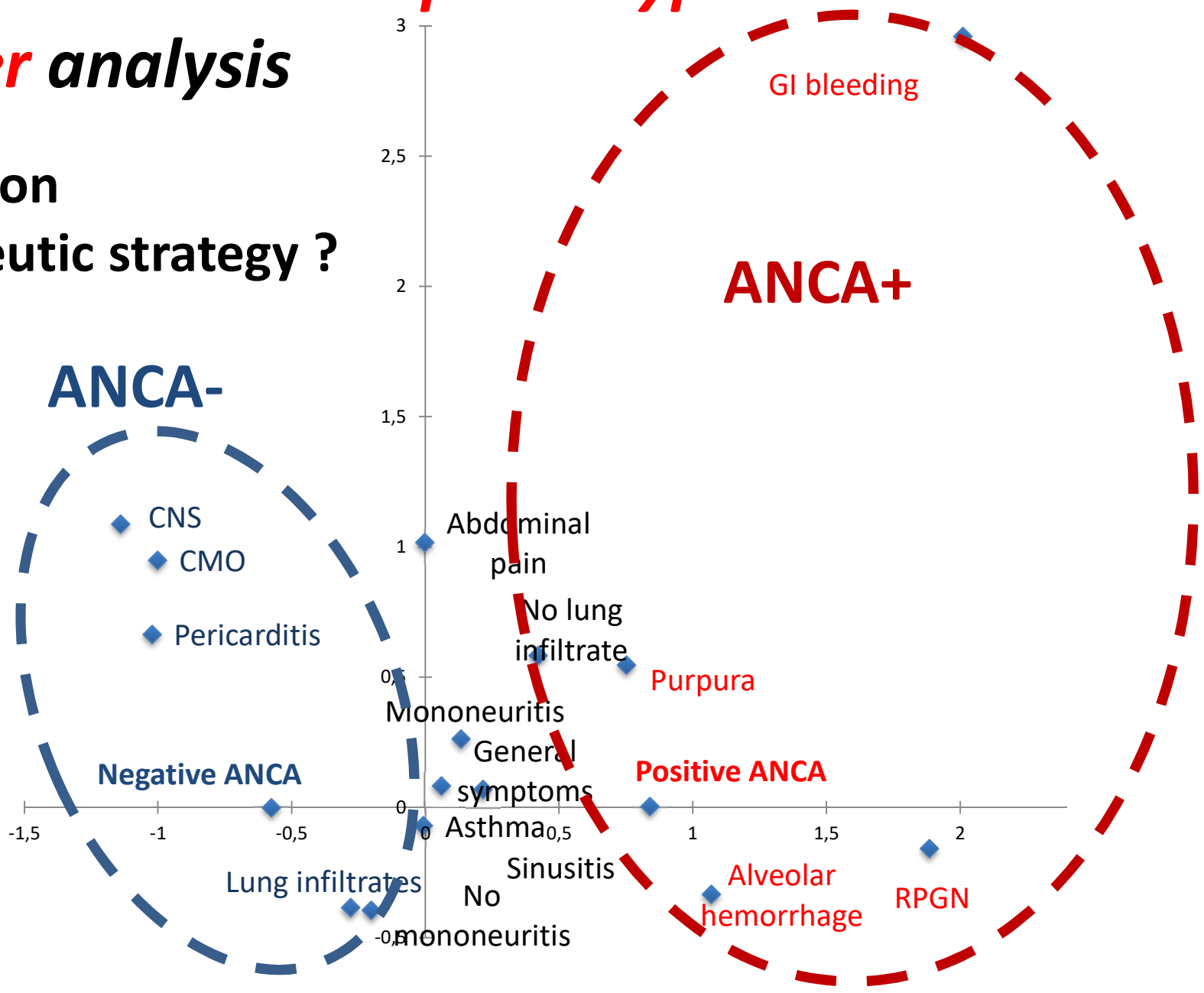
Cancer, infections, active vasculitis, respiratory events

Comarmond, Arthritis Rheum, 2013

EGPA : Two disease phenotypes

Cluster analysis

Impact on therapeutic strategy ?

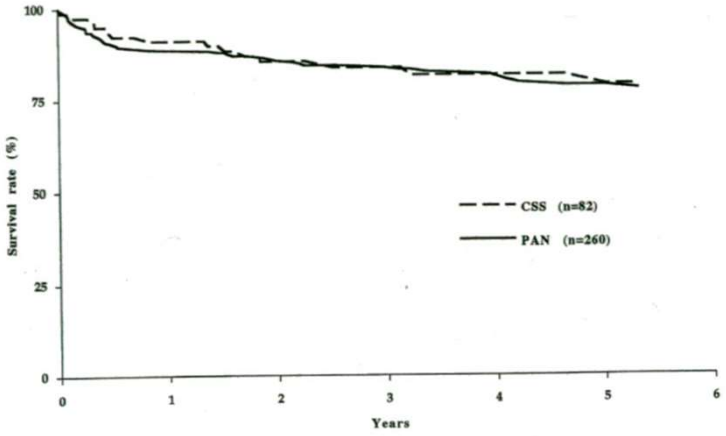


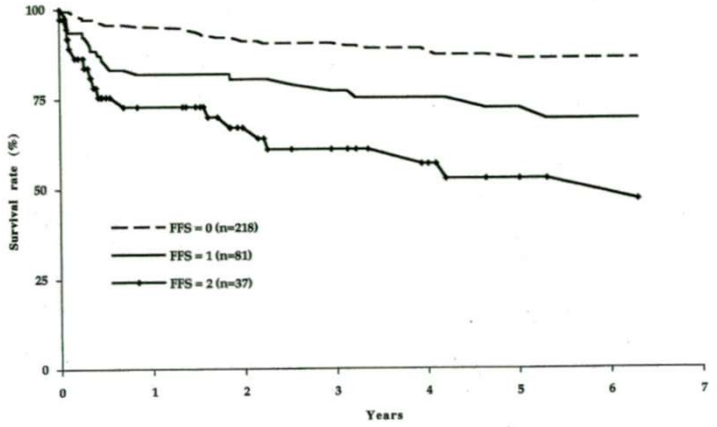
Prognostic Factors in Polyarteritis Nodosa and Churg-Strauss Syndrome

Guillevin L et al, Medicine, 1996;75:17-28

260 PAN and 82 EGPA
Identification of factors with significant poor prognostic value

Proteinuria >1 g/day
Serum creatinin >140 µmol/L
GI tract involvement
Cardiomyopathy
Central nervous system involvement





Treatment of Churg-Strauss Syndrome Without Poor-Prognosis Factors

Ribi C et al, Arthritis Rheum, 2008;58:586-94

Prospective multicenter randomized trial

1. To assess the efficacy of GCs alone as 1st-line treatment in EGPA without poor-prognosis factor (FFS=0)
2. To compare oral AZA versus intravenous CYC as adjuvant therapy for treatment failure or relapse

72 EGPA patients were included

At treatment failure or relapse, 19 patients were randomized to receive 6 months of oral AZA or 6 pulses of CYC

Results

93% achieved remission and 35% relapsed

Among the 19 patients randomized, 5/10 receiving AZA and 7/9 receiving pulse CYC achieved remission (P=NS)

At EOF, 79% whose disease was in remission required low-dose GCs to control respiratory disease

Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors

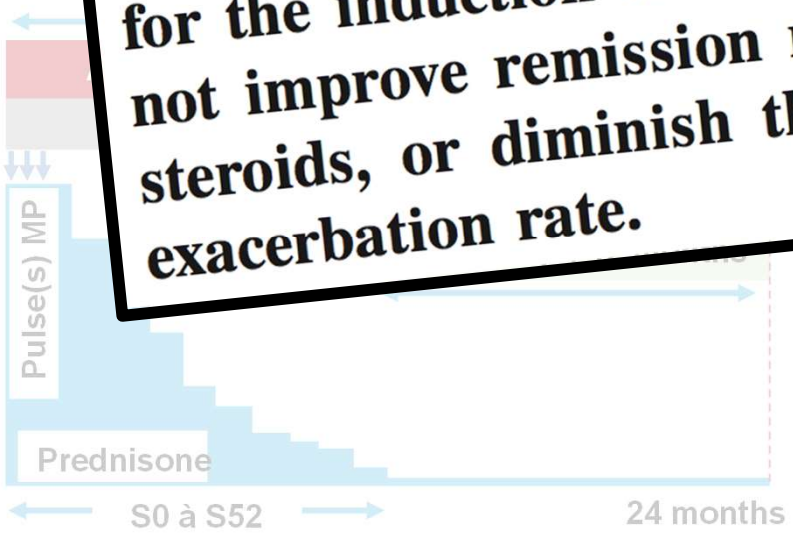
Puéchal X et al, Arthritis Rheumatol, 2017;69:2175-86

- 95 patients (EGPA: 51, MPA: 25, PAN: 19)
- Primary outcome: patients with refractory or relapsing dis

- Primary outcome at 24 months
  - Patients with relapse or refractory disease : AZA (n = 32) versus
  - Post-hoc analysis on EGPA patients → Same results

- Safety: no significant difference between groups

Conclusion. **Addition of AZA to glucocorticoids for the induction of remission of nonsevere SNVs does not improve remission rates, lower relapse risk, spare steroids, or diminish the EGPA asthma/rhinosinusitis exacerbation rate.**

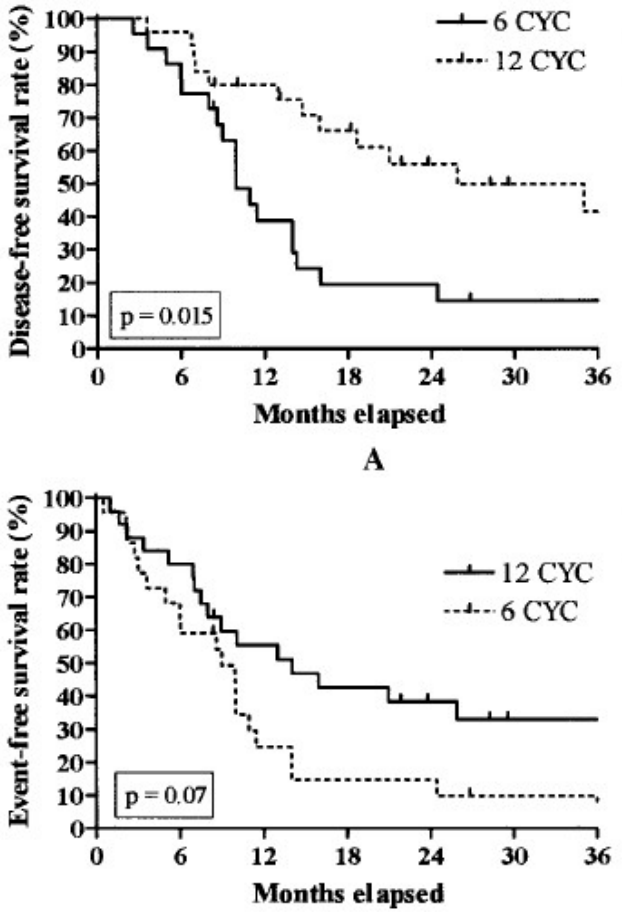


Churg-Strauss Syndrome With Poor-Prognosis Factors: A Prospective Multicenter Trial Comparing Glucocorticoids and Six or Twelve Cyclophosphamide Pulses in Forty-Eight Patients

Cohen P et al, Arthritis Rheum, 2007;57:686-93

Prospective multicenter trial including 48 EGPA patients with poor-prognosis factor (FFS ≥1)

Patients treated with GCs (1 mg/kg/day) and either 6 or 12 intravenous CYC pulses

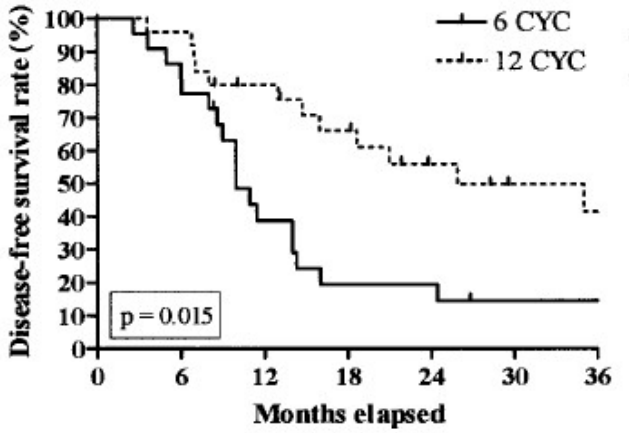


Churg-Strauss Syndrome With Poor-Prognosis Factors: A Prospective Multicenter Trial Comparing Glucocorticoids and Six or Twelve Cyclophosphamide Pulses in Forty-Eight Patients

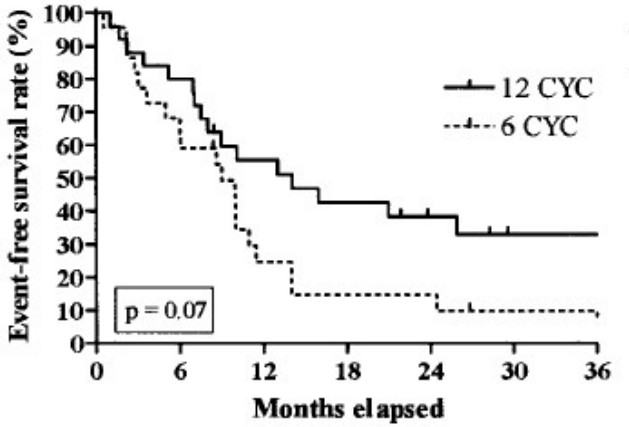
Cohen P et al, Arthritis Rheum, 2007;57:686-93

Need for a maintenance therapy to prevent relapses in EGPA patients with at least 1 poor-prognosis factor

Outcome	6-pulse CYC (n = 23)	12-pulse CYC (n = 25)	*P*
Clinical remission	21 (91.3)	21 (84)	NS
Failure	2 (8.7)	4 (16)	NS
Patients who relapsed	18 (78.2)	13 (52)	0.07
Major relapses	10 (55.5)	8 (61.5)	NS
Minor relapses†	14 (77.7)	6 (46.1)	0.02
Patients with severe side effect	11 (47.8)	13 (52)	NS
Deaths	2 (8.7)	2 (8)	NS



A



Treatment of EGPA before biologics era

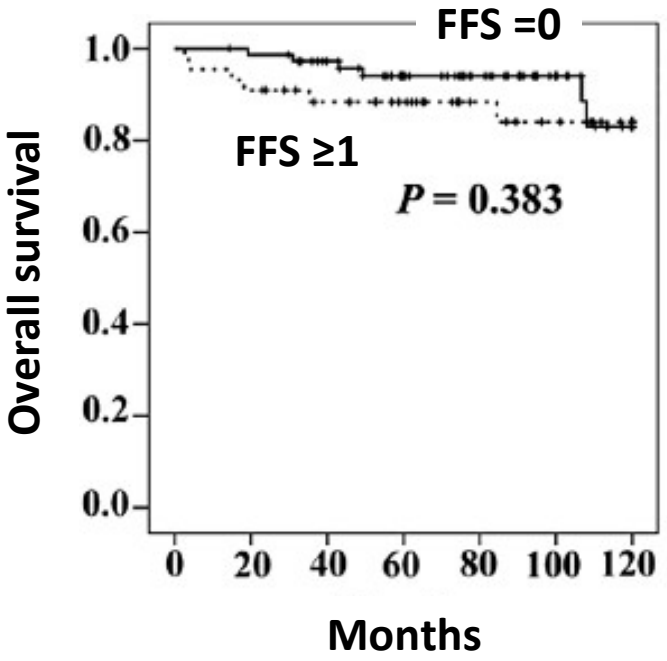
Therapeutic regimen based on prognosis stratification using Five Factor Score

	FFS = 0 (2/3)	FFS ≥ 1 (1/3)
Induction	GC 1 mg/kg/j	GC 1 mg/kg/j ± *Pulse MP* + CYC x 6-9
Maintenance	GC 18-24 months	GC + AZA or MTX 18-24 months

Long-term outcome with this regimen

Outcome

Initial remission achieved in 90%
Relapse in 35% (especially if ANCA+ and lower Eos)
Long-term remission in 29%
Death in 10% (especially ANCA-)



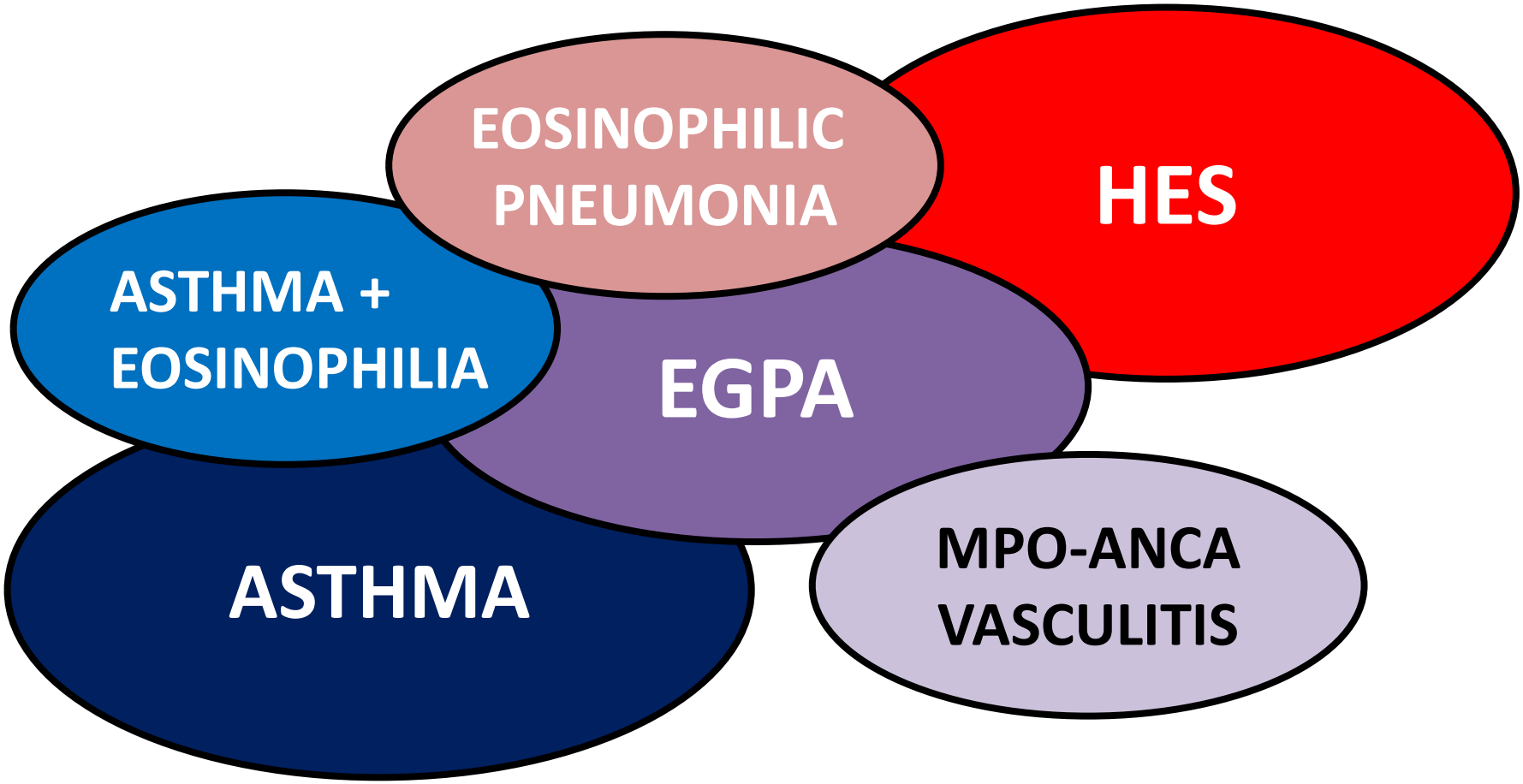
Sequelae in 86% of patients +++

Chronic asthma	**83%**
Peripheral neuropathy	**45%**
Nasal obstruction	**35%**
Osteoporosis	**30%**

85% patients were still on prednisone at last visit (mean follow-up 6 years) with a mean daily dose of 12 mg/day

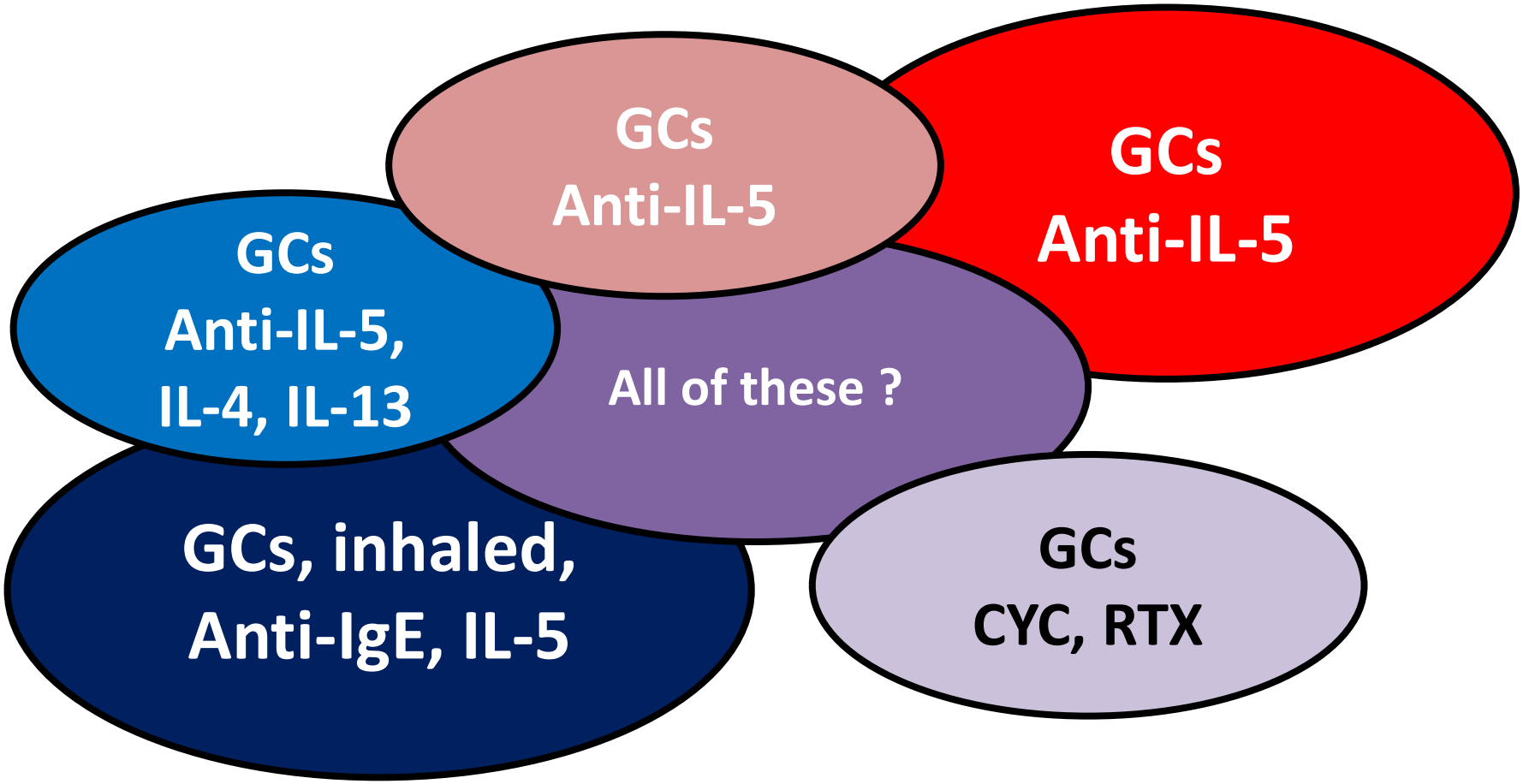
Samson, J Autoimmun, 2013
Comarmond, Arthritis Rheum, 2013

EGPA is a syndrome and not a unique disease



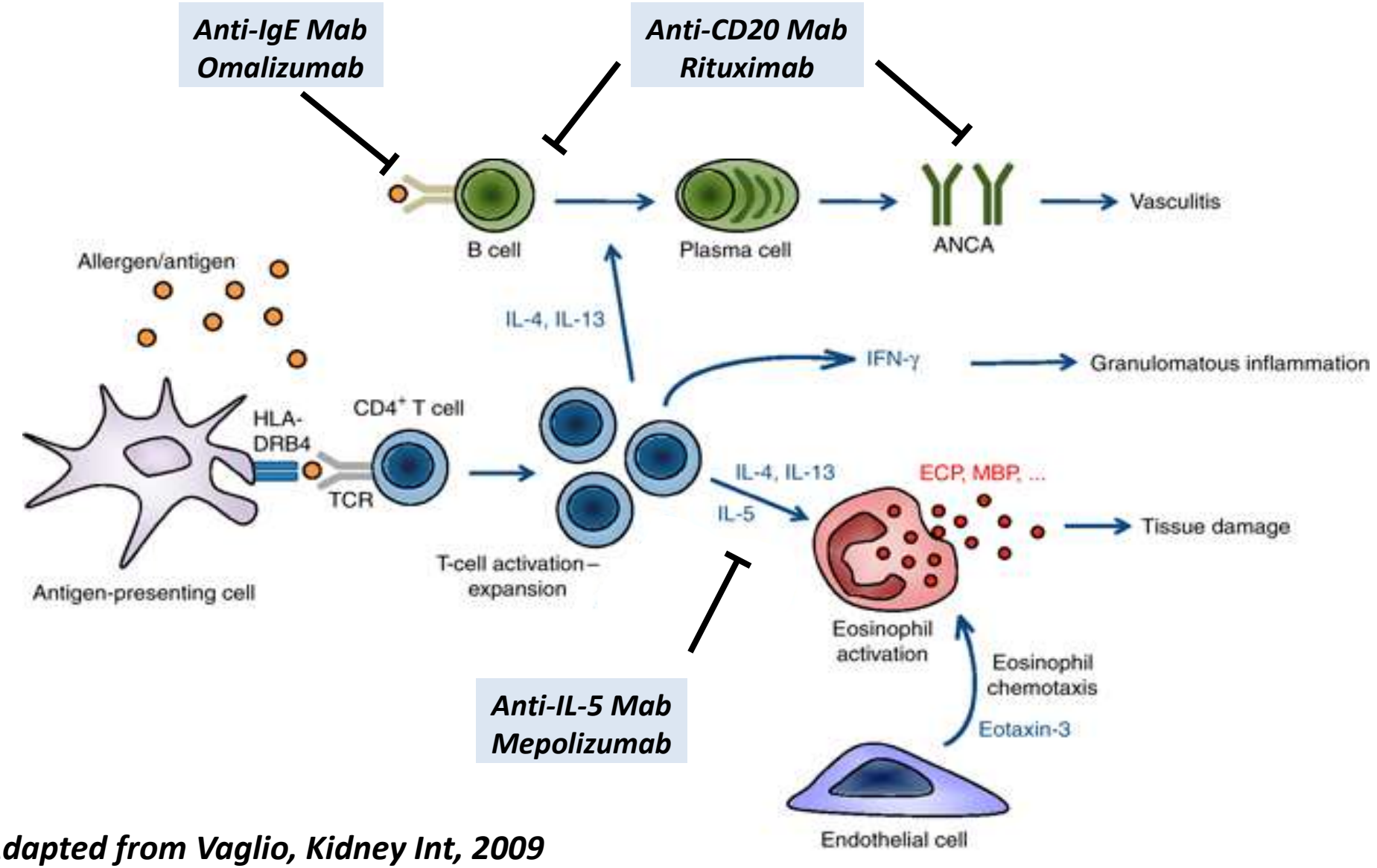
EGPA is at the crossroad of many diseases characterized by asthma, eosinophilia and vasculitis

Many potential therapeutic approaches



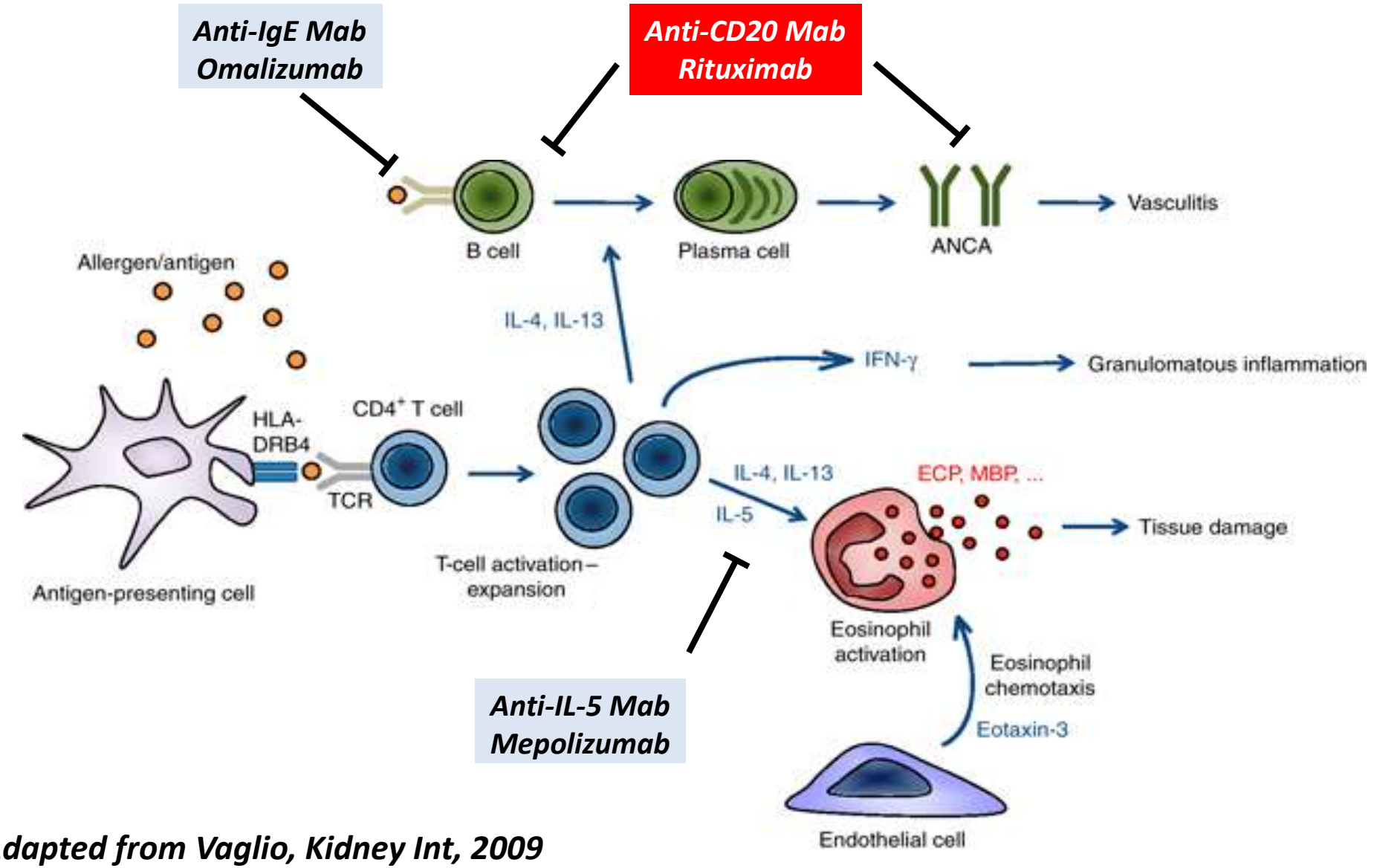
EGPA is at the crossroad of many diseases characterized by asthma, eosinophilia and vasculitis

Candidates for targeted therapies in EGPA



Adapted from Vaglio, Kidney Int, 2009

Candidates for targeted therapies in EGPA



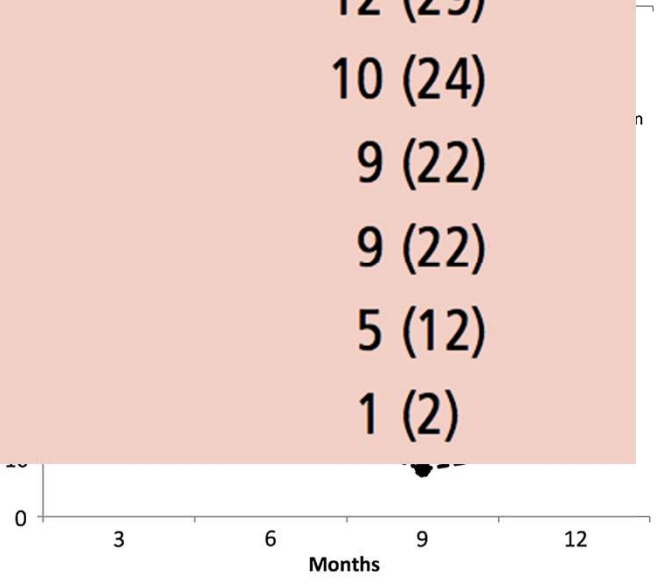
Adapted from Vaglio, Kidney Int, 2009

Annals of the Rheumatic

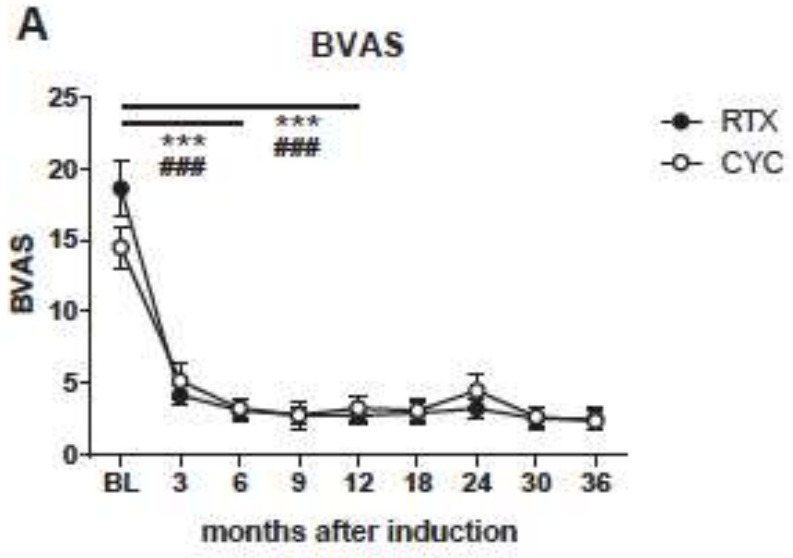
Rituximab for the treatment of eosinophilic

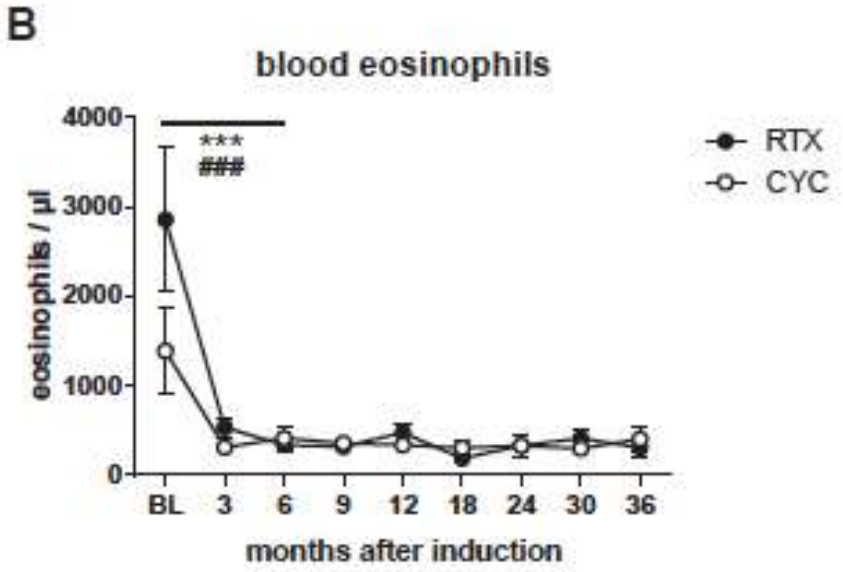
DEI score, median (IQR) at first rituximab treatment	8 (8–10)
BVAS median (IQR) at first rituximab treatment	11 (6–17.5)
Organ involvement according to DEI, number of patients (%)	
Lung (including asthma)	40 (98)
Ear, nose and throat	35 (85)
Arthralgia/arthritis	22 (54)
Skin	20 (49)
Peripheral nervous system	12 (29)
Renal	10 (24)
Gastrointestinal tract	9 (22)
Heart	9 (22)
Eyes	5 (12)
Central nervous system	1 (2)

Gastrointestinal tract 9 (22)
Heart 9 (22)
Eyes 5 (12)
Central nervous system 1 (2)

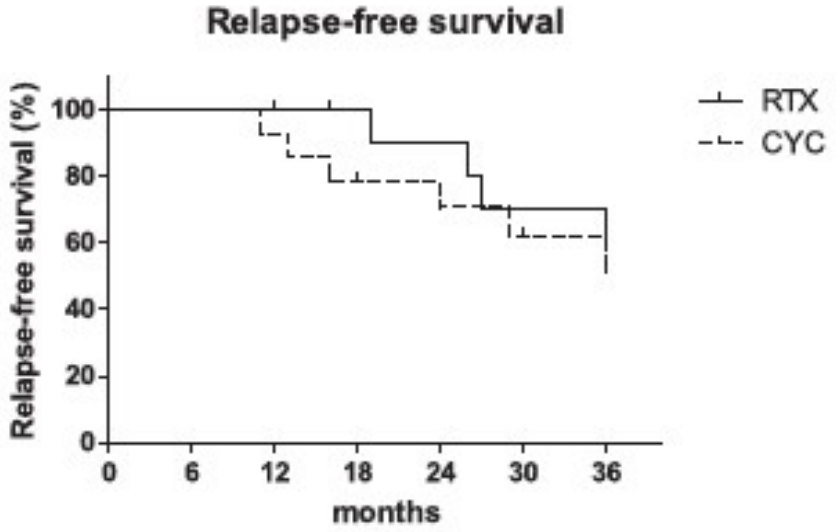


Rituximab as induction therapy in EGPA





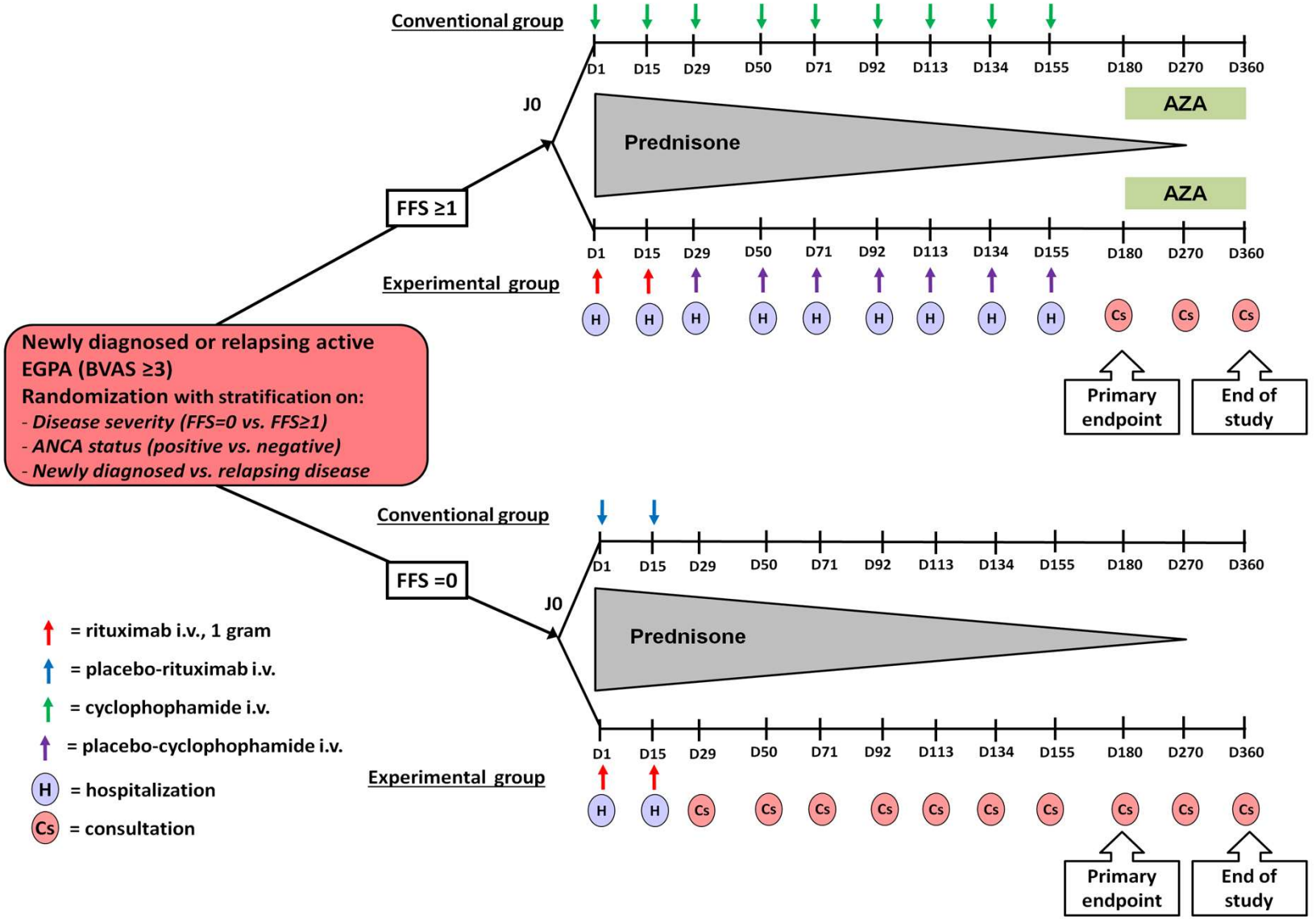
14 RTX-treated patients were compared with 14 age- and sex-matched patients treated with CYC for remission induction
64% of the RTX-treated patients had previously failed CYC treatment

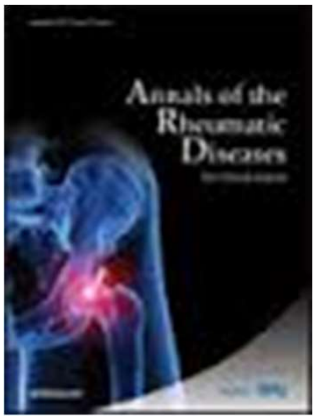


Thiel, J Allergy Clin Immunol Pract, 2017

Academic trial REOVAS

GFEV GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES



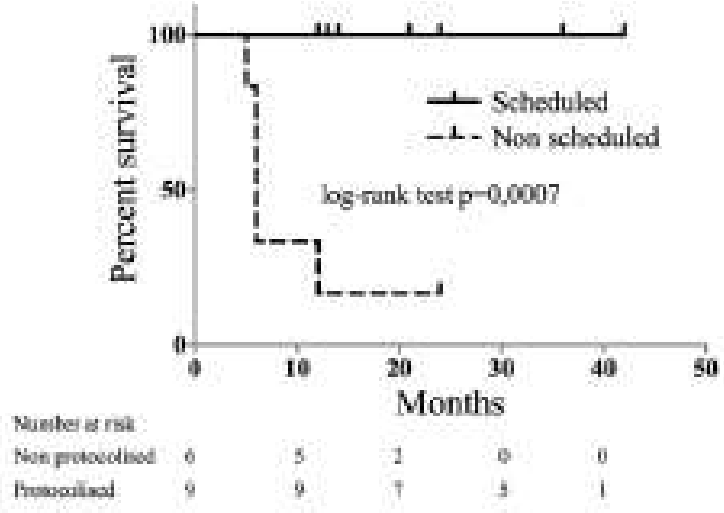


Scheduled rituximab maintenance reduces relapse rate in eosinophilic granulomatosis with polyangiitis

Emmi G et al, Ann Rheum Dis, 2017

20 EGPA patients treated with RTX as induction achieved remission in 75% at M3 (CR in 5 and PR in 10)
Among the 15 patients in remission:

- No scheduled RTX maintenance therapy in 6
- Scheduled RTX maintenance therapy in 9

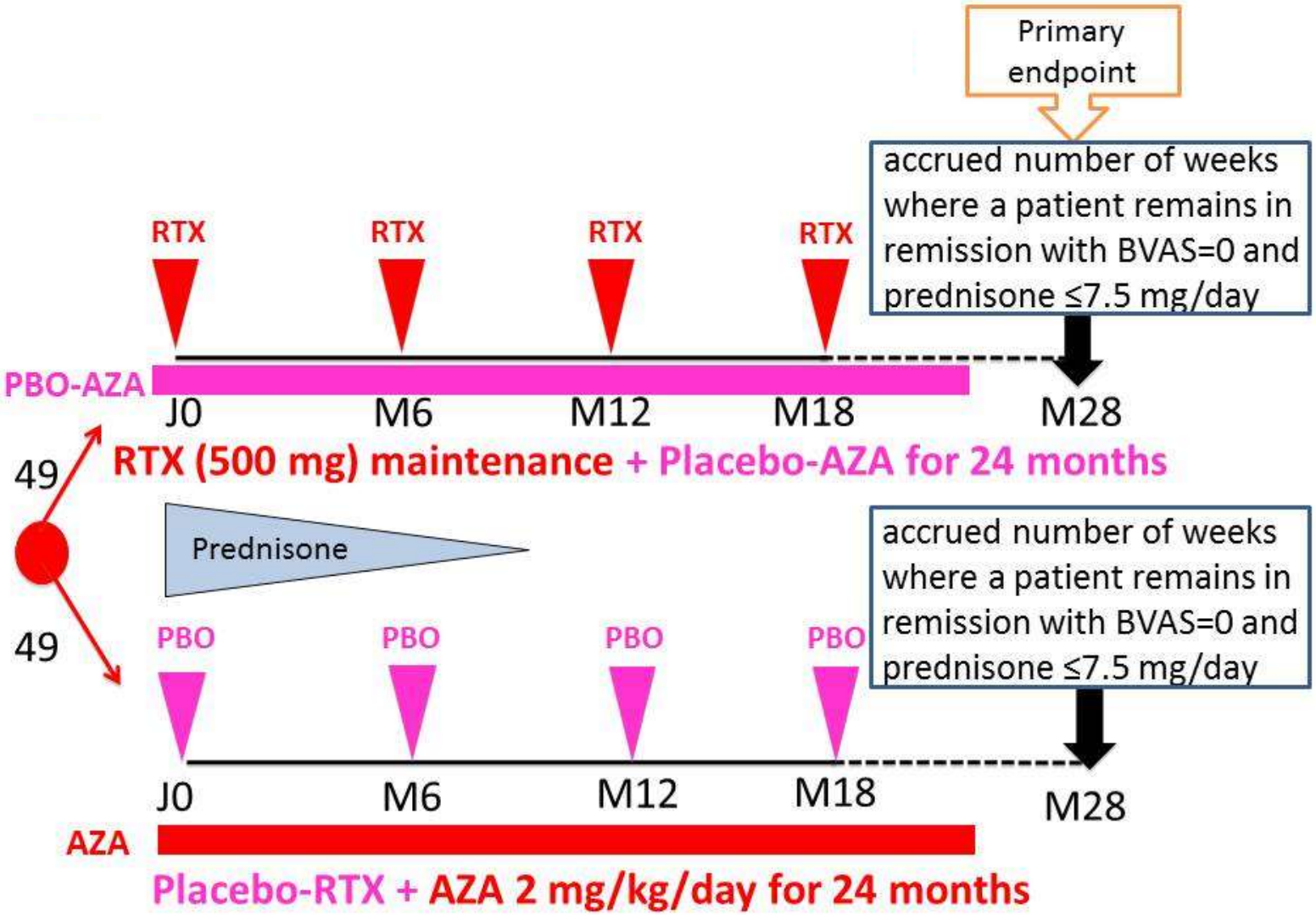


Discussion Rituximab demonstrated some efficacy in EGPA and led to a reduction in prednisolone requirement, but asthma and ENT relapse rates were high despite continued treatment. The ANCA positive subset appeared to have a more sustained response on isolated asthma/ ENT exacerbations.

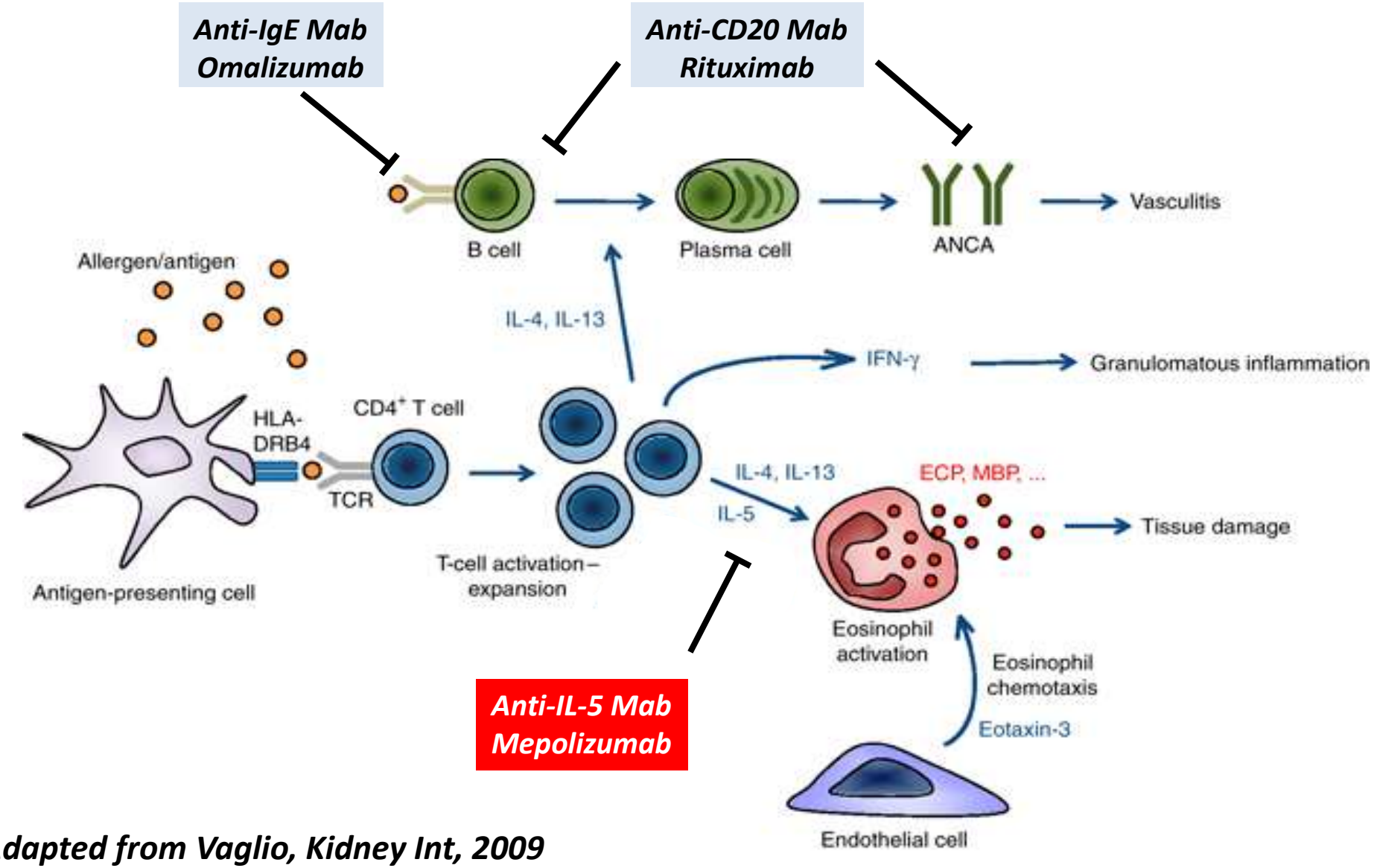
Teixeira, RMD Open, 2019

Academic trial MAINRITSEG

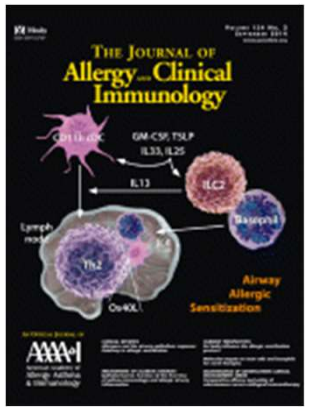
GFEV GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES



Candidates for targeted therapies in EGPA

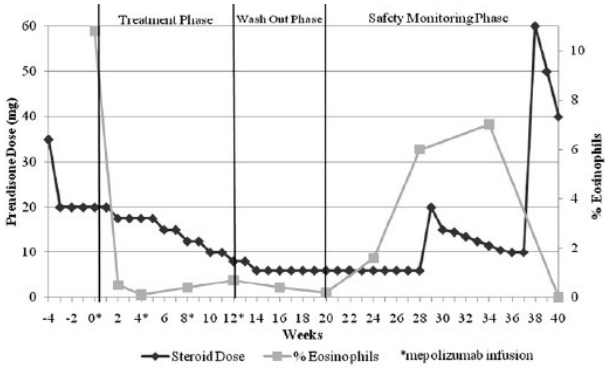


Adapted from Vaglio, Kidney Int, 2009



Kim S et al,
J Allergy Clin Immunol,
2010;125:1336-43

- 7 patients with GC >10 mg/d
- 4 infusions of MEPO
- Good tolerance
- ↓ Eos at W16 (from 3400 to 400/mm^3)
- ↓ GC at W16 (from 18.8 to 6.7 mg/d)
- Relapses at MEPO discontinuation

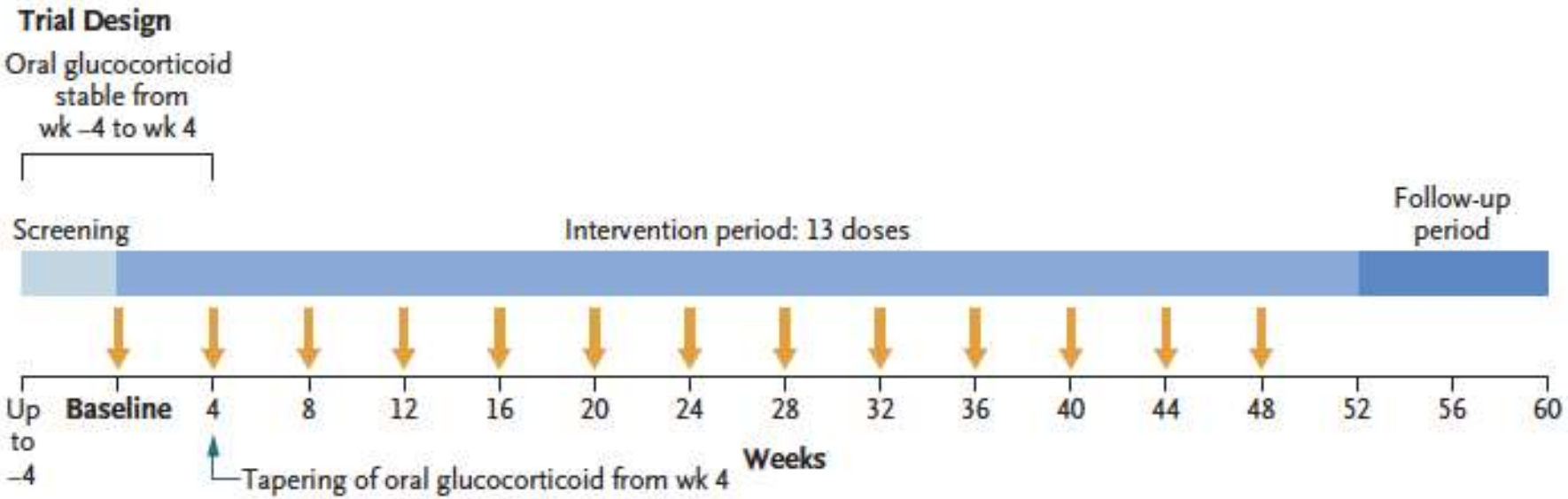


Moosig F et al,
Ann Intern Med,
2011;155:341-3

- 10 patients with refractory (n=3) or relapsing (n=7) disease
- BVAS > 3 under GC >12,5 mg/d + IS
- 9 monthly infusions of MEPO, then switch to methotrexate
- Remission (BVAS=0 and GC ≤7,5 mg/d) in 8/10 patients
- ↓ Eos and GC
- Relapses at MEPO discontinuation

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

Wechsler M et al, N Engl J Med, 2017;376:1921-32



Multicenter, double-blind, parallel-group, phase 3 trial
Randomization of EGPA patients with relapsing or refractory disease to receive <u>300 mg/month</u> of mepolizumab or placebo, plus standard care, for 52 weeks

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

Wechsler M et al, N Engl J Med, 2017;376:1921-32

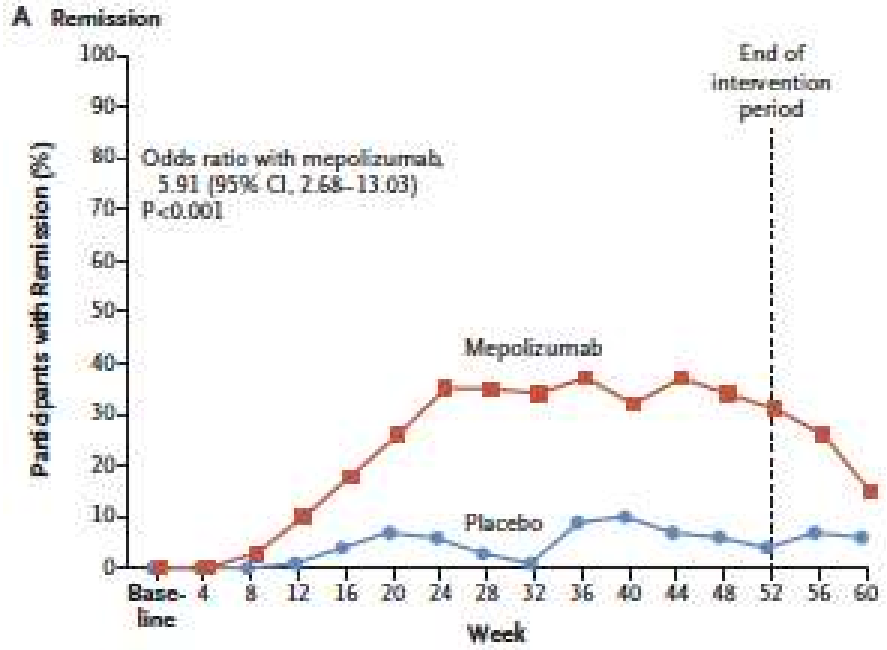
Characteristic	Mepolizumab (N=68)	Placebo (N=68)
ANCA-positive status — no. (%)†	7 (10)	6 (9)
Absolute eosinophil count per cubic millimeter‡	177±1.29	172±1.35
Prednisolone or prednisone dose — mg/day		
Median	12.0	11.0
Duration since diagnosis of EGPA — yr	5.2±4.4	5.9±4.9

In my point of view, patients were EGPA-related asthma rather than EGPA (with vasculitis and asthma)

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

Wechsler M et al, N Engl J Med, 2017;376:1921-32

Accrued weeks of remission over the 52-week period



Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

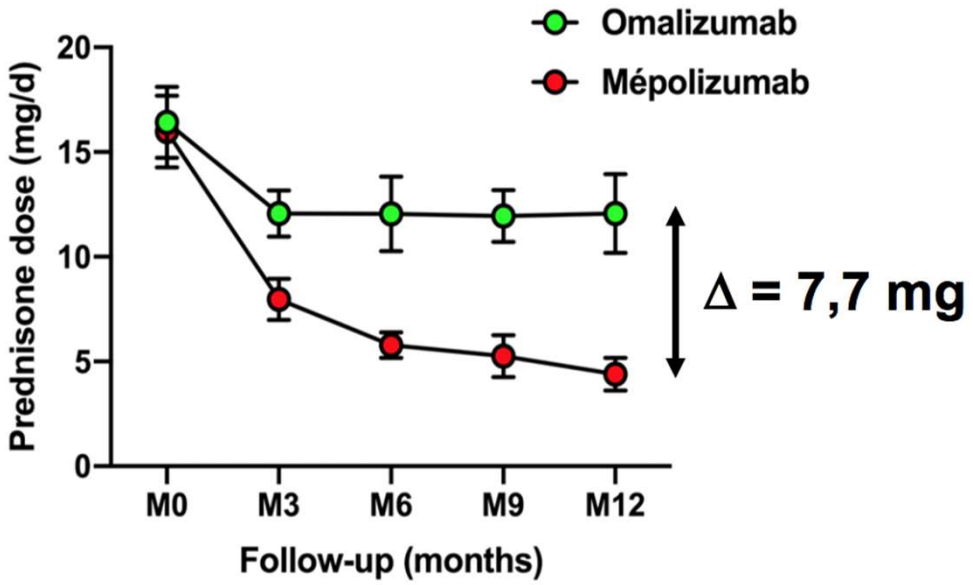
Wechsler M et al, N Engl J Med, 2017;376:1921-32

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

End Point	Mepolizumab (N=68)	Placebo (N=68)	Odds Ratio or Hazard Ratio (95% CI)	P Value
	no. of participants (%)			
Primary end points				
Accrued weeks of remission over 52-wk period			5.91 (2.68–13.03)	<0.001
0 wk	32 (47)	55 (81)		
>0 to <12 wk	8 (12)	8 (12)		
12 to <24 wk	9 (13)	3 (4)		
24 to <36 wk	10 (15)	0		
≥36 wk	9 (13)	2 (3)		
Remission at wk 36 and wk 48	22 (32)	2 (3)	16.74 (3.61–77.56)	<0.001
Other end points				
Remission within the first 24 wk that was sustained until wk 52	13 (19)	1 (1)	19.65 (2.30–167.93)	0.007
First EGPA relapse	38 (56)	56 (82)	0.32 (0.21–0.50)	<0.001

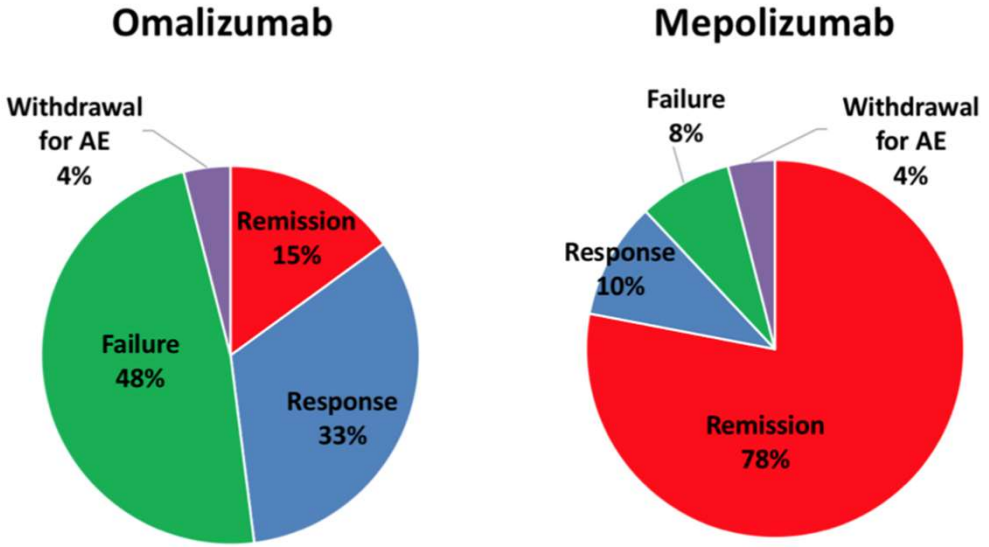
Response to therapy for the omalizumab and mepolizumab for GCs- dependent asthma

Mepolizumab has a much better GCs-sparing effect than omalizumab



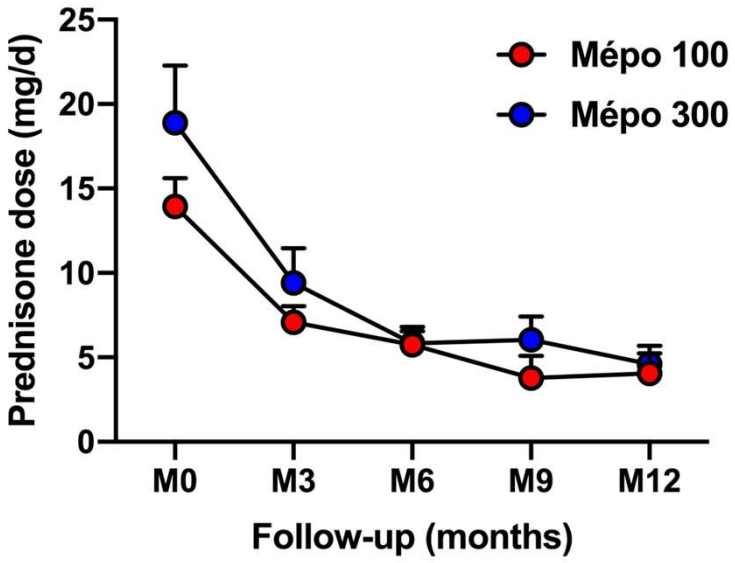
Remissions, partial responses, therapeutic failure and stop for adverse event were noted in :

- **15%, 33%, 48% and 4% for omalizumab**
- **78%, 10%, 8% and 4% for mepolizumab**

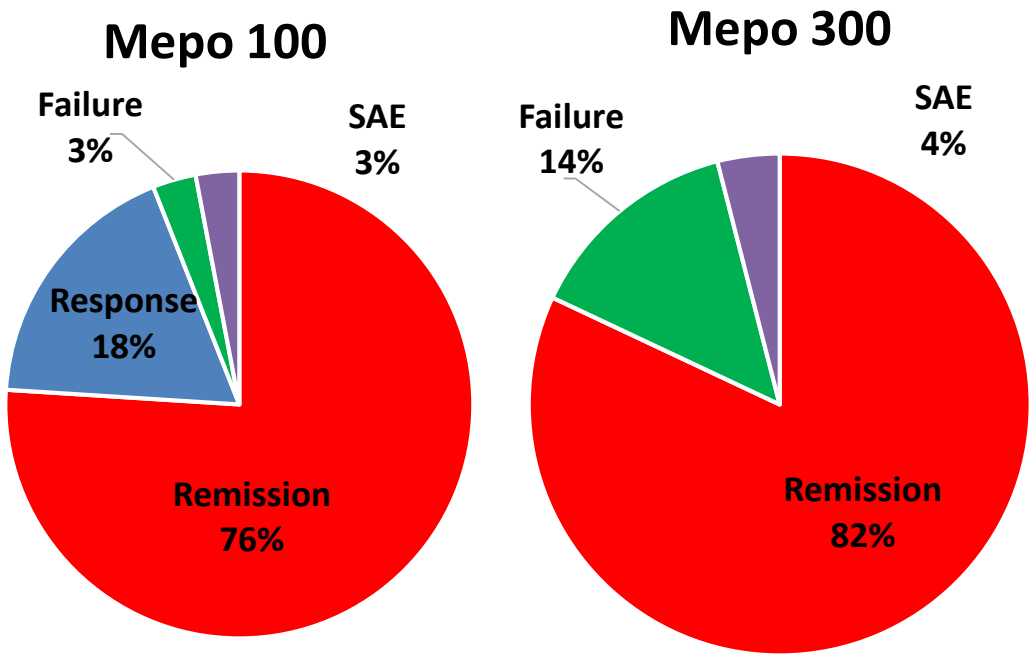


Response to therapy according to the dose of mepolizumab

Evolution of prednisone dose

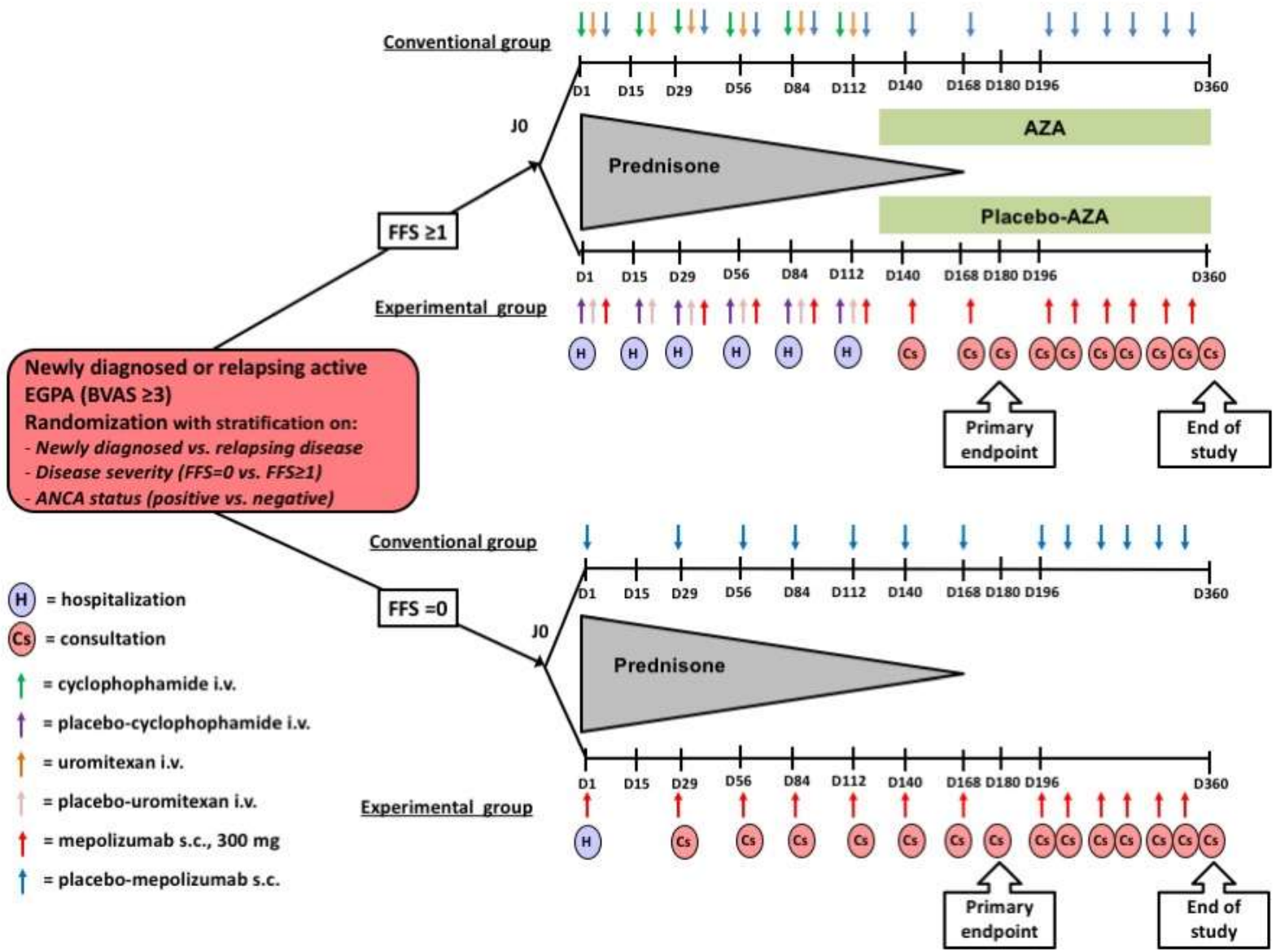


Overall response



Academic trial EMERGE

GFEV GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES



Towards a "personalized management" of EGPA patients

TSLP BIM CDK6 BACH2
GATA3 SOCS1 LPP TBX3

HLA-DQ GPA33, IL5

Anti-B cell therapy ? **Anti-IL-5 therapy ?**

Rituximab ***Mepolizumab***

Lyons, in press, Nat Commun

Take home messages

1. **Therapeutic stratification using FFS improved long-term EGPA overall survival**

2. **Therapeutic management using conventional immunosuppressive agents is associated with long-term use of GCs and sequelae (asthma and GCs-related)**

3. **Increasing interest of biologics in the treatment of EGPA but their place still needs to be defined**

4. **Mepolizumab represents to date the most effective agent to control EGPA-related asthma**

Acknowledgements

FVSG FRENCH VASCULITIS STUDY GROUP

Loïc Guillevin
Pascal Cohen
Xavier Puéchal

All investigators from the FVSG
All EGPA patients

Colleagues from the European EGPA Task Force