Treatmnet of Crescentic Glomerulonephritis

Iran University of Medical Scieneces

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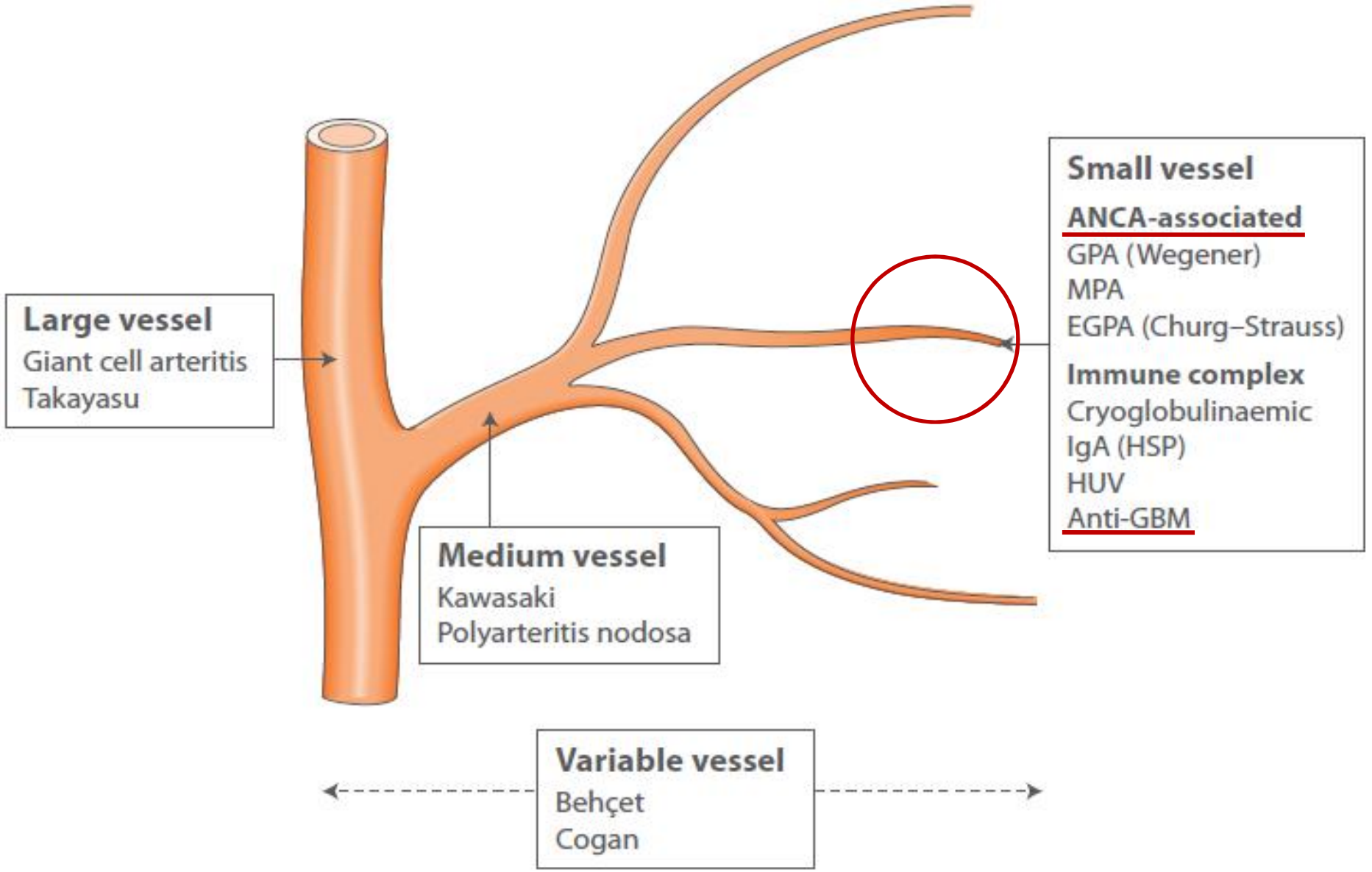
Agenda

ANCA-associated vasculitis :treatment and porgnosis

Anti-GBM antibody: treatment and prognosis disease:


Large vessel
Giant cell arteritis
Takayasu
Medium vessel
Kawasaki
Polyarteritis nodosa
Small vessel
ANCA-associated
GPA (Wegener)
MPA
EGPA (Churg–Strauss)
Immune complex
Cryoglobulinaemic
IgA (HSP)
HUV
Anti-GBM
Variable vessel
Behçet
Cogan

Rare diseases : combined incidence of 20 per million per year

With treatment, 85%–90% of patients will go into remission

Relapsing-remitting course

ESRD : 20% of patients at 5 years

5-year survival rate of approximately 75%

Arthritis Rheum. 2008;58:2908–2918.

Clinical assessment of AAV

Stage of the disease process

Distinction between active disease and damage

Quality-of-life (QOL) assessment.

Table 1 | Disease stages in ANCA-associated vasculitis

Disease stage	EUVAS and EULAR definition[53,61]	Systemic vasculitis outside ENT or lung	Threatened vital organ function	Serum creatinine (μmol/l)
Localized	Upper and/or lower respiratory tract disease without further systemic involvement or constitutional symptoms	No	No	<120
Early systemic	Any disease without organ-threatening or life-threatening involvement	Yes	No	<120
Generalized	Renal or other organ-threatening disease	Yes	Yes	<500
Severe	Renal or other vital organ failure	Yes	Organ failure	>500
Refractory	Progressive disease unresponsive to standard therapy	Yes	Yes	Any

Abbreviations: ANCA, antineutrophil cytoplasmic autoantibody; ENT, ear, nose, throat; EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Study Group.

Aims of treatment of GPA

Induction phase : rapidly reduce inflammation to control signs and symptoms of disease and prevent permanent tissue damage

maintenance phase : lower-dose immunosuppression is used to prevent relapse

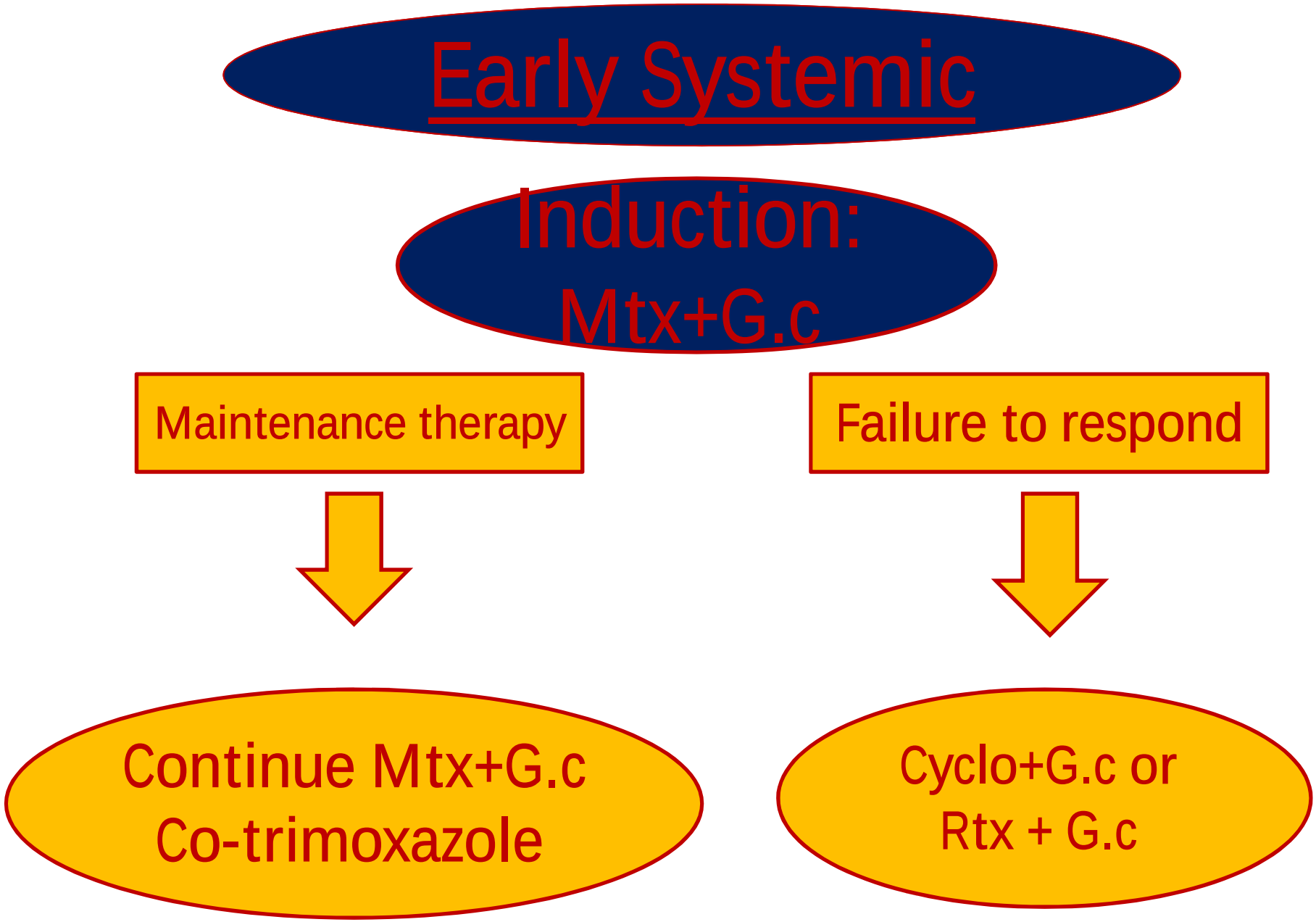
↓immunosuppression → improvements in outcome over the past 30 years

Table 2 | Randomized controlled trials for induction of remission in AAV using cytotoxic or biological agents

Disease stage	Trial (patients)	Inclusion criteria	Treatment groups (dose)	Primary end points	Outcome
Early systemic	NORAM[18] (100)	New diagnosis of GPA or MPA, and creatinine <150 µmol/l	Methotrexate (0.3 mg/kg once weekly) versus daily oral cyclophosphamide	Remission Time to relapse	Methotrexate not inferior to cyclophosphamide Time to relapse shorter with methotrexate
Generalized	CYCLOPS[16] (149)	New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150–500 µmol/l	Intravenous pulse cyclophosphamide (15 mg/kg) versus daily oral cyclophosphamide (2 mg/kg)	Remission Time to relapse	Pulse cyclophosphamide not inferior to oral cyclophosphamide Less leucopenia and trend towards more relapses with pulse cyclophosphamide
Generalized	RITUXVAS[32] (44)	New diagnosis of AAV and severe renal involvement	Rituximab (four 375 mg/m^2 infusions) plus two intravenous pulses of cyclophosphamide, versus intravenous pulse cyclophosphamide only	Sustained remission	Rituximab not inferior to pulse cyclophosphamide
Generalized	RAVE[33] (198)	New or relapsing GPA or MPA	Rituximab (4 x 375 mg/m^2 infusions) versus daily oral cyclophosphamide	Complete remission and cessation of glucocorticoids at 6 months	Rituximab not inferior to oral cyclophosphamide Rituximab better in patients with relapse than after first diagnosis

NORAM Study

De Groot, K. *et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 52, 2461–2469 (2005).*


Early Systemic
Induction:
Mtx+G.c
Maintenance therapy
Failure to respond
Continue Mtx+G.c
Co-trimoxazole
Cyclo+G.c or
Rtx + G.c

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Cyclops study

Groups did not differ in time to remission:hazard ratio, 1.098 [95% CI, 0.78 to 1.55]; P = 0.59

proportion of patients who achieved remission at 9 months : 88.1% vs. 87.7%

There was no difference in mortality or renal function at the end of the study.

Ann. Intern. Med. 150, 670–680 (2009)

Table 4 | Pulse cyclophosphamide reduction based on renal function and age[16]

Age (years)	Cyclophosphamide dose reduction (per pulse, mg/kg)	
	Creatinine <300 µmol/l	Creatinine 300–500 µmol/l
<60	15	12.5
60–70	12.5	10
>70	10	7.5

Cyclophosphamide	Neutropenia Lymphopenia Bacterial infection *Pneumocystis jirovecii* pneumonia Hemorrhagic cystitis Teratogenicity	Gonadal failure, 4.1%* Bone marrow failure, 3%* Hypogammaglobulinemia[128] Bladder cancer (SIR 2.4)[47] Myeloid leukemia (SIR 3.2)[47] Nonmelanoma skin cancer (SIR 2.8)[47]
Rituximab	Infection Allergic reactions Reactivation of hepatitis B (check status before starting)	Progressive multifocal leukoencephalopathy (rare <1:10,000)[92] Hypogammaglobulinemia (repeated doses or prior immunosuppression)[128]
Azathioprine (check TPMT before starting)	Lymphopenia Liver blood test abnormalities Rash Infection	Associated with nonmelanoma skin cancer[108,109]
Methotrexate (avoid if eGFR <30 mL per minute)	Nausea/gastrointestinal side effects Abnormal liver blood tests Macrocytosis Leukopenia Infection Teratogenicity	Lung injury (<1%)[129] Liver injury (unusual if liver tests monitored and action taken if abnormal)
Mycophenolate mofetil	Gastrointestinal upset Leukopenia Infection Teratogenicity	Not clear whether risk of skin or lymphoproliferative malignancy increased

B-Cell Depletion

Equal effectiveness of rituximab and cyclophosphamide (oral or IV) for remission induction in two RCTs:

Jones, R. B. *et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N. Engl. J. Med. 363, 211–220 (2010).*
Stone, J. H. *et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N. Engl. J. Med. 363, 221–232 (2010).*

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Table 3. Comparison of trial design and preliminary data from the RITUXVAS and RAVE studies

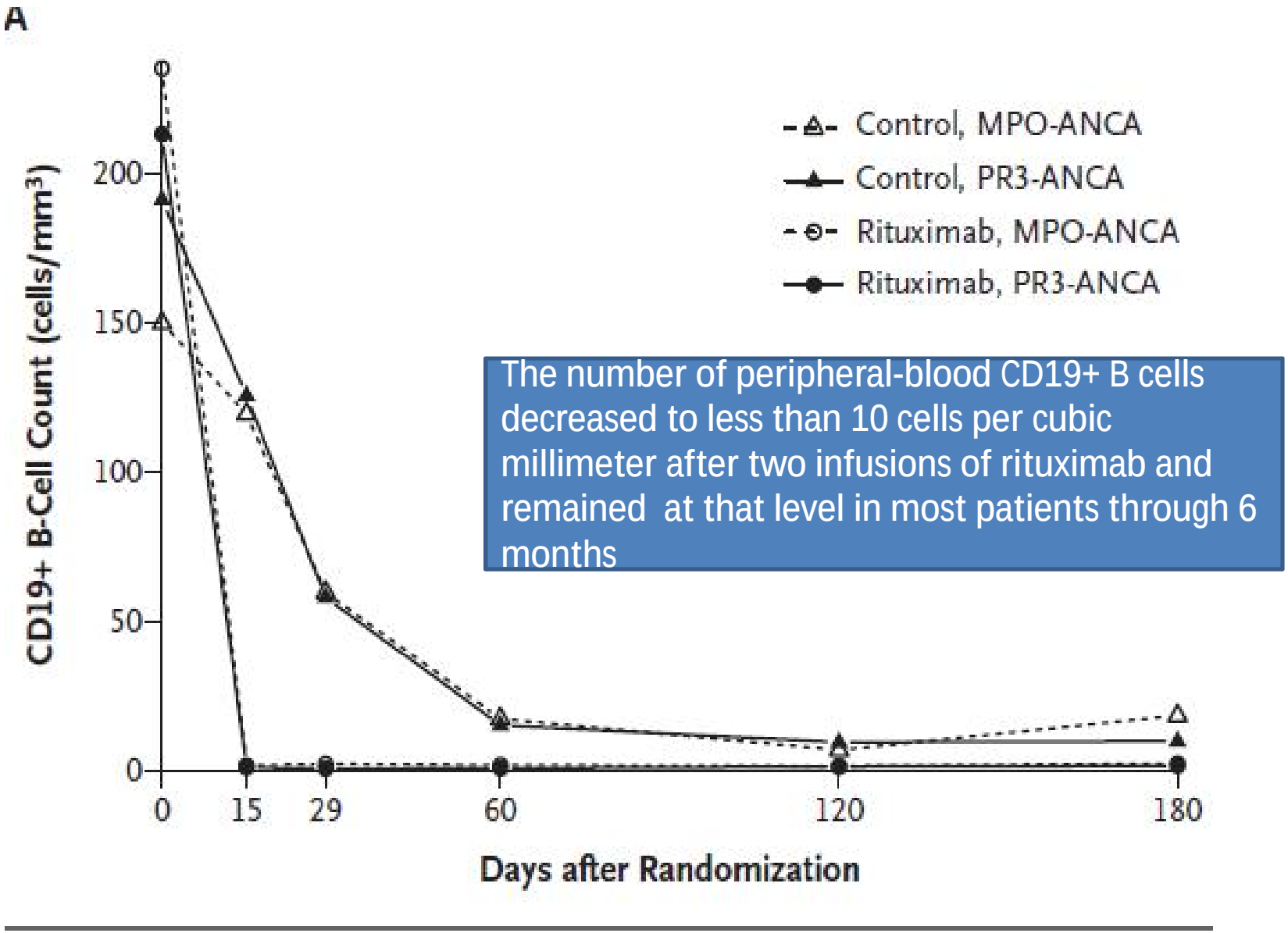
	RITUXVAS trial [42]	RAVE trial [43]
Patients (*n*)	44 – 33 RTX, 11 CYC	197 – 99 RTX, 98 CYC
New diagnosis (%)	100	49
Wegner's granulomatosis:microscopic polyangiitis	1:1	3:1
PR3:myeloperoxidase (%)	58:42	67:33
Median age (years), RTX:CYC	68:67	54:51.5
Mean Birmingham Vasculitis Activity Score at entry, RTX:CYC	19:18	8.5:8.2
Renal function at entry, RTX:CYC	20:12 (GFR)	54:69 (creatinine clearance)
Rituximab dose	375 mg/m^2×4 + two i.v. CYC pulses	375mg/m^2×4
CYC dose	15 mg/kg i.v., six to 10 cycles	2 mg/kg/day per orally
Plasma exchange	Yes	No
Steroid dose	1 g i.v. methylprednisolone	1 to 3 g i.v. methylprednisolone
	1 mg/kg/day prednisolone per orally	1 mg/kg/day prednisolone per orally
	Decrease to 5 mg/day by 6/12	Decrease to 40 mg/day by 1/12
		Stop prednisolone by 6/12
Maintenance therapy	CYC → AZA at 3 to 6 months	CYC → AZA at 3 to 6 months
	RTX → none	RTX → none
Primary endpoints	12 months	6 months
Remission (%), RTX:CYC	76:82	64:53 (no prednisolone)
		71:62 (<10 mg prednisolone)
Median time to remission (days), RTX:CYC	90:94	NR
Serious adverse events (%), RTX:CYC	42:36	22:33
Deaths, RTX:CYC	6:1	1:2
GFR at end of study, RTX:CYC	39:27	NR

RAVE Study

Sixty-three of the 99 patients in the rituximab group (64%) reached the primary end point, as compared with 52 of 98 in the control group (53%).

The treatment difference of 11 percentage points between the groups met the criterion for noninferiority (P<0.001)

Evidence of the superior efficacy of rituximab among patients with relapsing disease at baseline persisted even after adjustment for differences in ANCA type and clinical site (odds ratio, 1.40; 95% CI, 1.03 to 1.91; P = 0.03)



The number of peripheral-blood CD19+ B cells decreased to less than 10 cells per cubic millimeter after two infusions of rituximab and remained at that level in most patients through 6 months

Table 3 | Recommendations for inducing remission of AAV according to EULAR and BSR[59,60]

Disease stage	Treatment	Dose
Localized	Co-trimoxazole with or without glucocorticoids	960 mg, twice daily
Localized	Methotrexate and glucocorticoids	Methotrexate 15 mg per week (oral or subcutaneous), increasing to 20–25 mg per week, plus folic acid and glucocorticoids
Early systemic	Methotrexate and glucocorticoids	Methotrexate 15 mg per week (oral or subcutaneous), increasing to 20–25 mg per week, plus folic acid and glucocorticoids
Generalized	Cyclophosphamide and glucocorticoids	Intravenous pulse cyclophosphamide (three pulses of 15 mg/kg every 2 weeks, then every 3 weeks, for a total of 6–9 pulses) and glucocorticoids or Oral cyclophosphamide 2 mg/kg and glucocorticoids, duration 3–6 months
Generalized	Rituximab and glucocorticoids	Rituximab four infusions of 375 mg/m^2 once a week
Severe	Plasma exchange as adjunctive therapy to cyclophosphamide or rituximab (standard therapy)	Seven rounds of plasma exchange 60 ml/kg bodyweight

BSR, British Society of Rheumatology; EULAR, European League Against Rheumatism

Four once-weekly infusions of 375 mg/m² or Two 1 g infusions, 2 weeks apart seem to be equally effective for induction of remission,
The concomitant glucocorticoid regimen that is most appropriate for use with any remission-inducing agent is unclear.

For patients with organ-threatening or life-threatening disease, treatment with rituximab alone has not yet been tested.
Cyclophosphamide might be added to rituximab therapy in patients with severe and/or life-threatening AAV

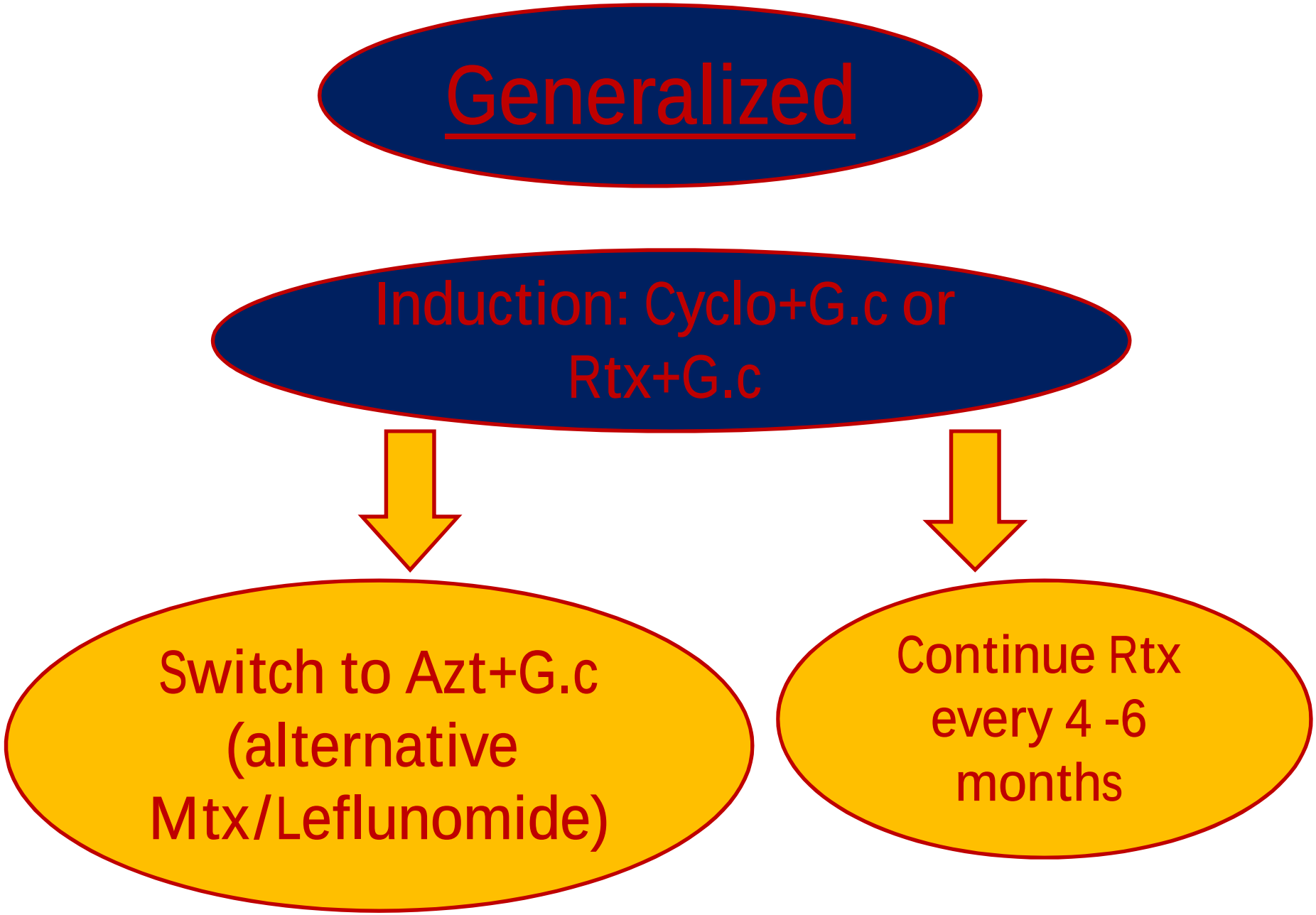
-Continued

Patients with relapse who were PR3-ANCA-positive did better on rituximab than on cyclophosphamide.

Patients who cannot tolerate cyclophosphamide

Those who are of reproductive age

Whose disease activity is poorly controlled or relapse while taking cyclophosphamide.


Generalized
Induction: Cyclo+G.c or Rtx+G.c
Switch to Azt+G.c (alternative Mtx/Leflunomide)
Continue Rtx every 4 -6 months

Generalized with RPGN	MEPEX[24] (137)	New diagnosis of GPA or MPA and creatinine >500 µmol/l	Plasma exchange and oral cyclophosphamide versus 3 × intravenous methylprednisolone pulse and oral cyclophosphamide	Renal survival at 3 months	Better renal survival with plasma exchange 24% risk reduction for ESRD with plasma exchange
MPA, GPA	MYCYC[23] (140)	New diagnosis of GPA, MPA and major organ involvement	Mycophenolate mofetil (2–3 g daily) versus intravenous pulse cyclophosphamide (15 mg/kg)	Remission at 6 months Relapse	Preliminary data: noninferiority not proven for mycophenolate mofetil versus pulse cyclophosphamide
MPA, GPA, EGPA or PAN	CORTAGE[46] (104)	New diagnosis of MPA, GPA, EGPA, PAN and age >65 years	Rapid glucocorticoid tapering and reduced-dose intravenous pulse cyclophosphamide (500 mg) versus standard intravenous pulse cyclophosphamide (500 mg/m²)	Severe adverse events	Preliminary data: less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates

MYCYC Study

46/70 of the MMF
48/70 of the Cyclo

→ Remission

Risk of relapse is higher in MMF group

(clinivaltrials.gov identifier NCT00414128)

Jones, R. B. A randomized trial of mycophenolate mofetil versus cyclophosphamide for remission induction of ANCA-associated vasculitis

Plasma Exchange

Severe renal involvment

Alveolar haemorrhage

Refractory or relapsing disease

Anti-GBM antibody positivity

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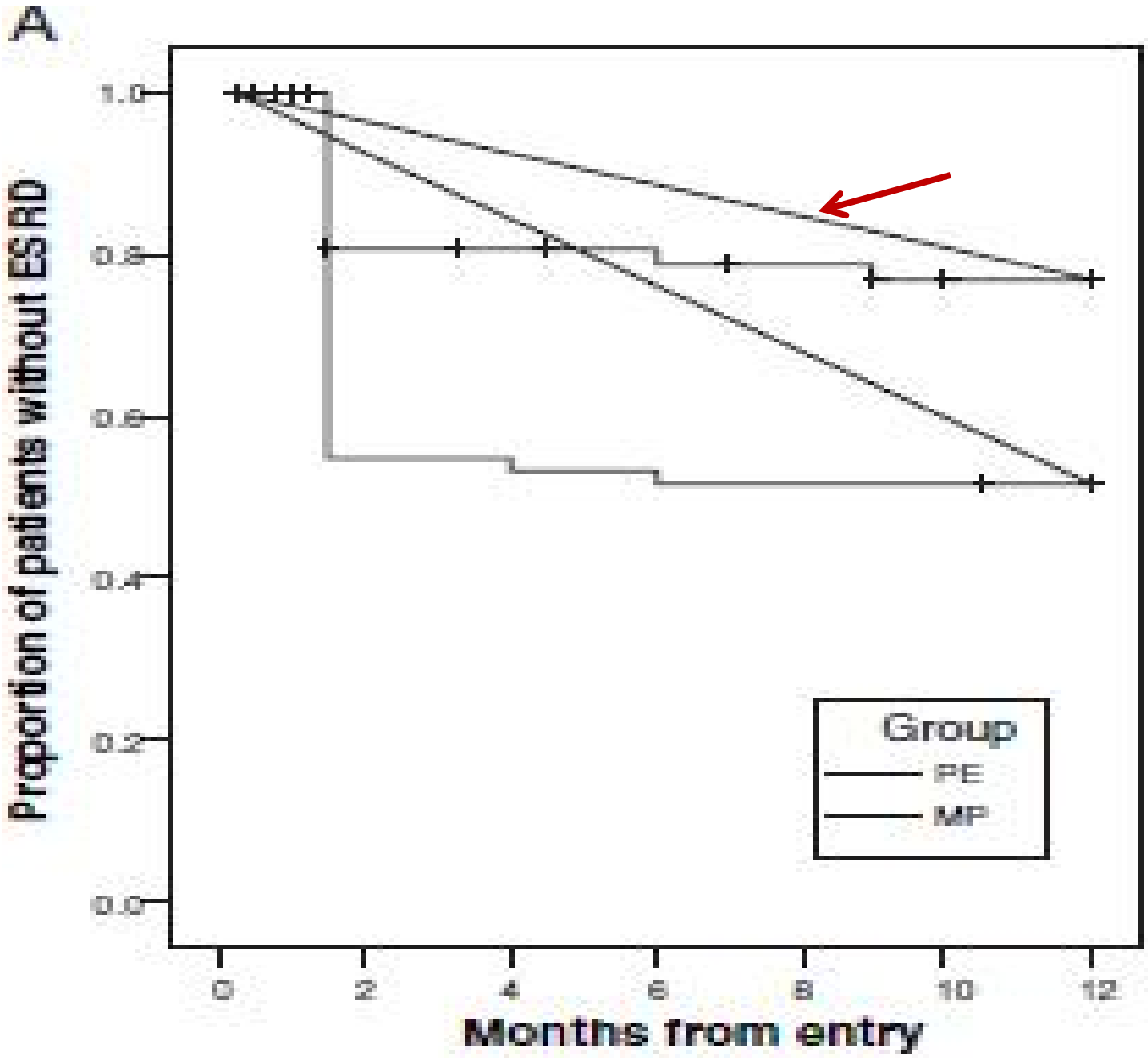
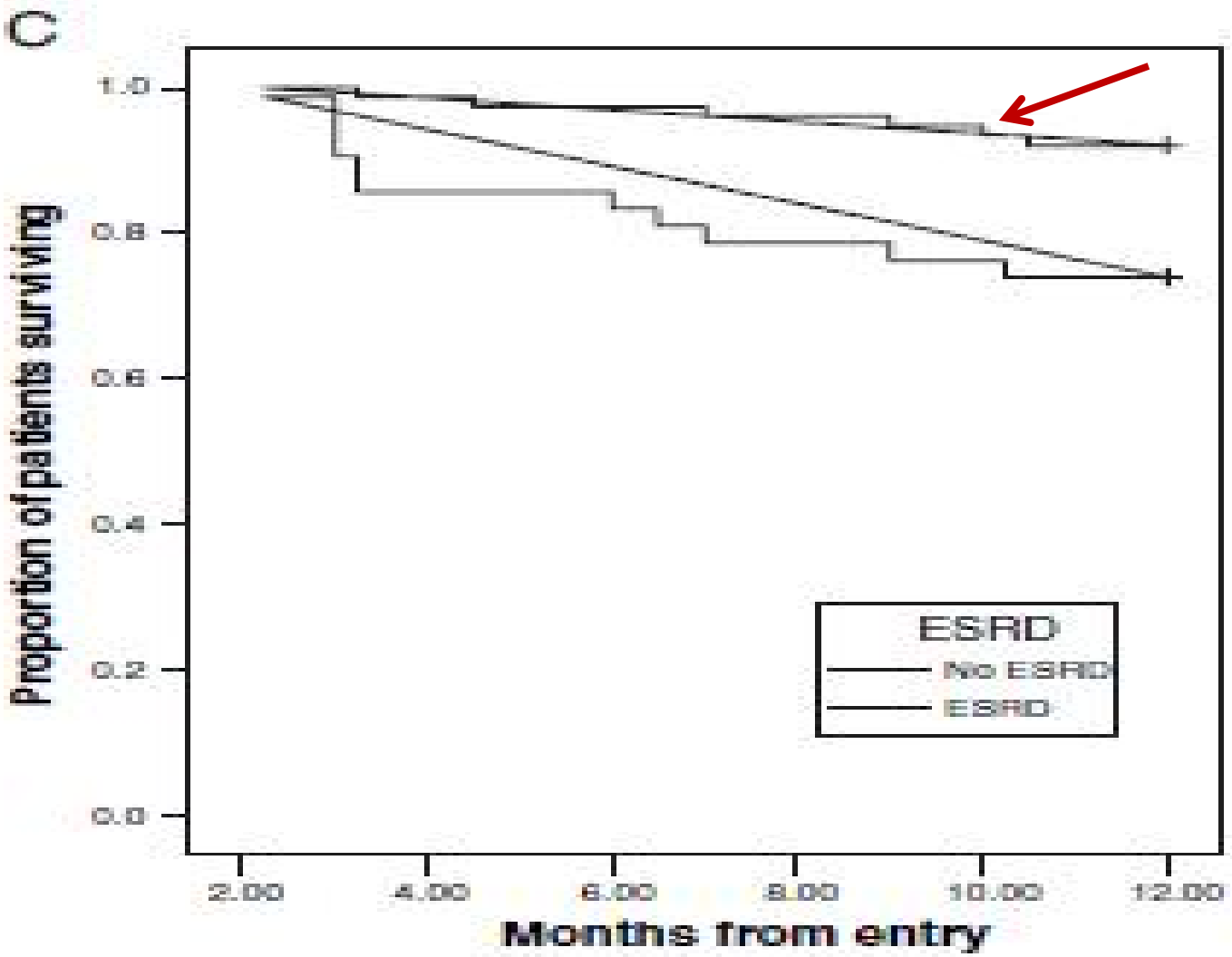
MEPEX Study

At 3 months, the proportion of dialysis-independent patients was significantly higher in the plasma exchange group than in the methylprednisolone group (69% versus 49%; *P = 0.02).*

PE was also associated with a decreased risk of ESRD at 12 months (19% versus 43%).

Jayne, D. R. *et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J. Am. Soc. Nephrol. 18, 2180–2188 (2007).*


A
Proportion of patients without ESRD
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
Months from entry
Group
PE
MP


C
Proportion of patients surviving
1.0
0.8
0.6
0.4
0.2
0.0
2.00
4.00
6.00
8.00
10.00
12.00
Months from entry
ESRD
No ESRD
ESRD

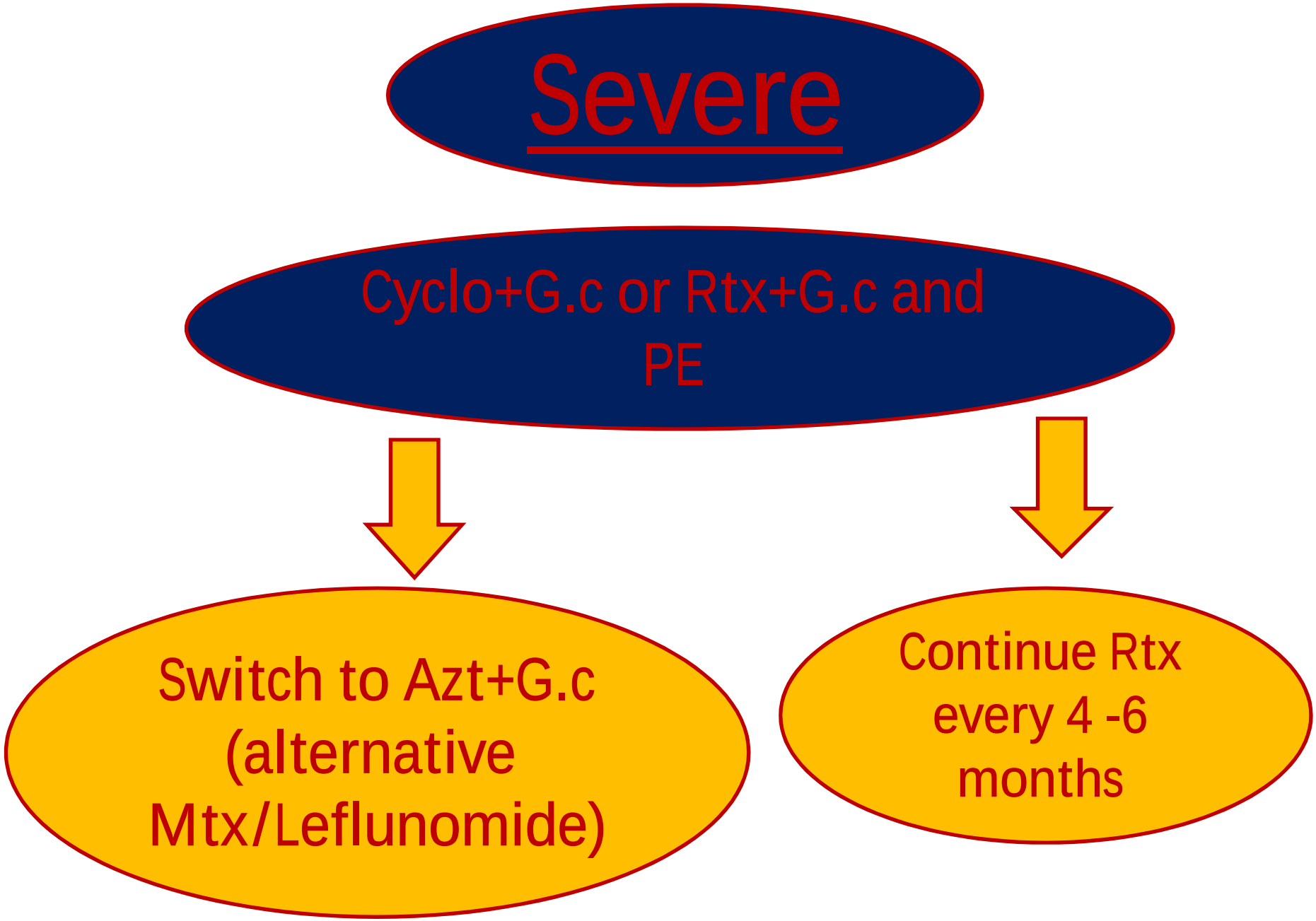
($P = 0.005$).

PEXIVAS trial

Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) - Associated Vasculitis (*NCT00987389* , n=500)

This study is currently recruiting participants (GFR<50 ml/min and or alveolar haemorrhage).

Sponsor: University of Pennsylvania


Severe
Cyclo+G.c or Rtx+G.c and PE
Switch to Azt+G.c (alternative Mtx/Leflunomide)
Continue Rtx every 4 -6 months

Therapeutic approach to ANCA-negative AAV

Controlled, prospective studies on the treatment of patients with ANCA-negative pauci-immune crescentic glomerulonephritis are not available. In general, the guidelines for ANCA-positive disease are also used for ANCA-negative disease.

Table 4 Trials of induction therapy in AAV in progress or completed and not yet published

Trial	Indication (total projected n)	Induction (trial)	Induction (control)	Primary endpoint	Trial number
Induction trials					
MYCYC[61]	New onset GPA or MPA (n=140)	MMF and Pred (n=70)	IV Cyc and Pred (n=70)	Remission at 6 months	NCT00414128
PEXIVAS[66]	Renal MPA or GPA (GFR <60 mL per minute) or pulmonary hemorrhage (n=500)	Plex + standard or reduced Pred + Cyc or Rtx (n=250)	Plex + standard or reduced Pred + Cyc or Rtx (n=250)	Composite of all-cause mortality and ESRD	NCT00987389
CLEAR[67]	Renal GPA or MPA (GFR >25mL per minute, n=60)	CCX168 + Cyc + half dose or no Pred	Cyc + standard Pred	Safety of CCX168 (secondary corticosteroid use)	NCT01363388
SPARROW[130]	Relapsed GPA (n=216)	Gusperimus and Pred	Cyc and Pred or rituximab and Pred or MTX and Pred	Proportion of patients in complete or partial remission	NCT01446211
ALEVIATE[118]	Refractory GPA or MPA (n=24)	Alemtuzumab 30 mg on day 1 and 2 at 0 and 6 months (high dose)	Alemtuzumab 15 mg on day 1 and 2 at 0 and 6 months (low dose)	Proportion of patients in complete or partial remission	NCT01405807

Disease activity

BVAS

active disease as abnormalities due to vasculitis that are new or have worsened within the past 4 weeks.

VDI: irreversible change resulting from scars

(for at least 3 months and the VDI score can either increase or remain stable over time)

PEXIVAS – Birmingham Vasculitis Activity Score for WG Vasculitis (BVAS/WG) FORM 19

Participant Initials:	F M L	Evaluation Date:	D D / M M / Y Y Y Y
Study ID:		Investigator:	

Please select Assessment Point: ☐ Baseline Assessment

☐ Week 2 Assessment	☐ Week 4 Assessment	☐ Week 8 Assessment	☐ Week 12 Assessment	☐ Week 26 Assessment	☐ Week 39 Assessment	☐ Week 52 Assessment	☐ 6 monthly Assessment

Instructions:
Tick box (☐ or O) only if abnormality is ascribable to the presence of active AAV: Wegener's Granulomatosis or Microscopic Polyangiitis.
☐ Tick box only if the abnormality is **persistent disease activity** since the last assessment and not worse within the **previous 28 days.**
O Tick box only if the abnormality since the last assessment is **newly present or worse** within the **previous 28 days.**
Δ If no items are present in any section, tick "none".
Major items are in bold and marked with an *.
All AAV-related clinical features need to be documented on this form if they are related to active disease.
Use "OTHER" category as needed.

	Persistent	New/Worse	Not Present	None
1. General				Δ
a. arthralgia/arthritis	☐	O	( )	
b. fever (≥ 38 degrees °C)	☐	O	( )	
2. CUTANEOUS				Δ
a. purpura	☐	O	( )	
b. skin ulcer	☐	O	( )	
c. ***gangrene**	☐	O	( )	
3. MUCOUS MEMBRANES/EYES				Δ
a. mouth ulcers	☐	O	( )	
b. conjunctivitis/episcleritis	☐	O	( )	
c. retro-orbital mass/proptosis	☐	O	( )	
d. uveitis	☐	O	( )	
e. ***scleritis**	☐	O	( )	
f. ***retinal exudates/haemorrhage**	☐	O	( )	
4. EAR, NOSE & THROAT				Δ
a. bloody nasal discharge /nasal crusting / ulcer	☐	O	( )	
b. sinus involvement	☐	O	( )	
c. swollen salivary gland	☐	O	( )	
d. subglottic inflammation	☐	O	( )	
e. conductive deafness	☐	O	( )	
f. ***sensorineural deafness**	☐	O	( )	

	Persistent	New/Worse	Not Present	None
5. CARDIOVASCULAR				Δ
a. pericarditis	☐	O	( )	
6. GASTROINTESTINAL				Δ
a. ***mesenteric ischemia**	☐	O	( )	
7. PULMONARY				Δ
a. pleurisy	☐	O	( )	
b. nodules or cavities	☐	O	( )	
c. other infiltrate secondary to WG	☐	O	( )	
d. endobronchial involvement	☐	O	( )	
e. ***alveolar haemorrhage**	☐	O	( )	
f. ***respiratory failure**	☐	O	( )	
8. RENAL				Δ
a. hematuria (no RBC casts) (≥ 1 + or ≥ 10 RBC/hpf)	☐	O	( )	
b. ***RBC casts and/or glomerulonephritis**	☐	O	( )	
Note: If both hematuria and RBC casts are present, score only the RBC casts (the major item).				
c. ***rise in creatinine > 30% or fall in creatinine clearance > 25%**	☐	O	( )	
9. NERVOUS SYSTEM				Δ
a. ***meningitis**	☐	O	( )	
b. ***cord lesion**	☐	O	( )	
c. ***stroke**	☐	O	( )	
d. ***cranial nerve palsy**	☐	O	( )	
e. ***sensory peripheral neuropathy**	☐	O	( )	
f. ***motor mononeuritis multiplex**	☐	O	( )	
10. OTHER (describe all items and * items deemed major)				Δ
a.	☐	O	( )	
b.	☐	O	( )	
c.	☐	O	( )	
d.	☐	O	( )	

11. TOTAL NUMBER OF ITEMS:			
a	b	c	d
Major New/Worse	Minor New/Worse	Major Persistent	Minor Persistent

DETERMINING DISEASE STATUS	12. CURRENT DISEASE STATUS (check all that apply)	
Severe Flare: ≥ 1 new/worse Major item	a. Severe flare/new disease	☐
Limited Flare: ≥ 1 new/worse Minor item	b. Limited flare/new disease	☐
Persistent Disease: Continued (but not new/worse) activity	c. Persistent disease	☐
Remission: No active disease, including either new /worse or persistent items	d. Remission	☐

Table 1 | Are ANCA present in all patients with AAV?

Diagnosis	PR3-ANCA	MPO-ANCA	Elastase-ANCA	No ANCA detected	% of patients with ANCA
GPA (*n*=364)	323	25	4	12*	96
EGPA (*n*=36)	0	23	0	13	64
MPA (*n*=85)	16	67	1	1	98
NCGN (*n*=54)	4	47	1	2	94

Rheumatology (Oxford). 2012;51:100–109.

Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis—a meta-analysis

Gunnar Tomasson[1], Peter C. Grayson[1], Alfred D. Mahr[2], Michael LaValley[3] and Peter A. Merkel[1]

Abstract

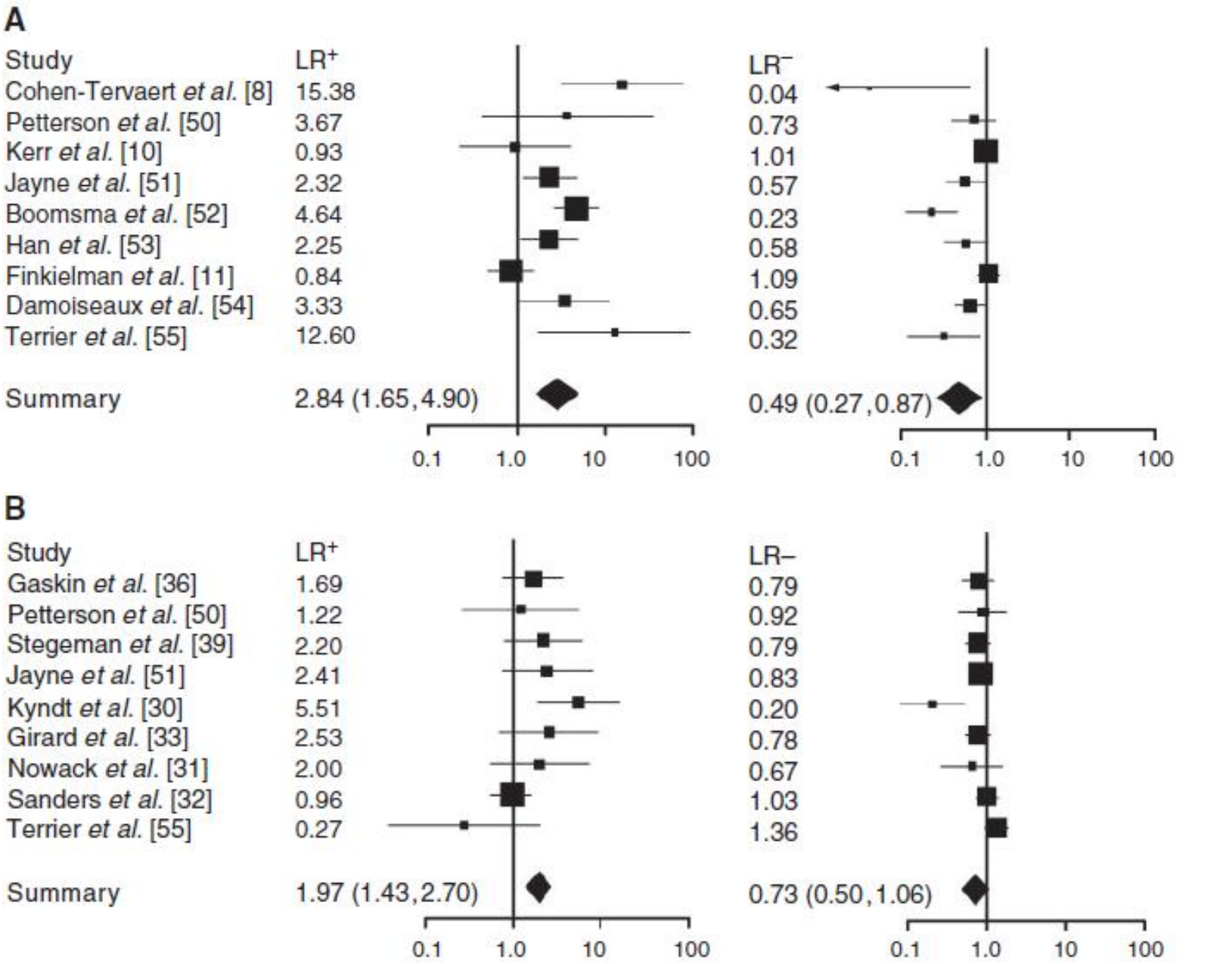
Objective. The value of repeated ANCA measurements among patients with an established diagnosis of ANCA-associated vasculitis (AAV) remains controversial. The aim of this study was to explore whether either of the two distinct patterns of ANCA values during remission, a rise in ANCA or persistently positive ANCA, predicted future relapse.

Methods. MEDLINE and EMBASE searches were performed. Studies with at least 10 subjects with AAV from which both sensitivity and specificity of a rise in ANCA and/or persistent ANCA for future disease relapse could be calculated were included. Likelihood ratios were calculated for each study and pooled to arrive at summary estimates. I^2-values were calculated as a measure of heterogeneity and meta-regression was used to explore sources of heterogeneity.

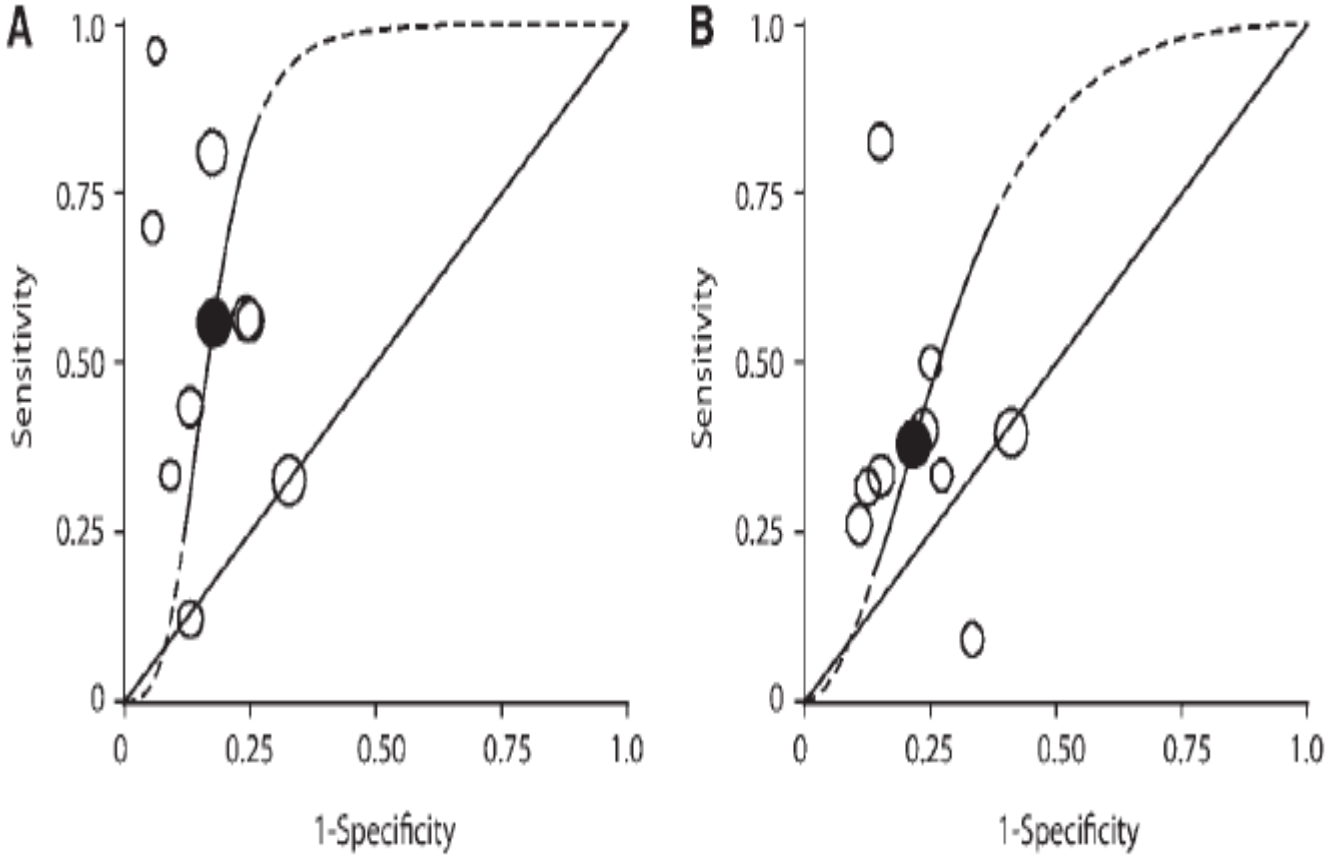
Results. Nine articles on a rise in ANCA and nine articles on persistent ANCA were included. The summary estimates for positive likelihood ratio ($LR+$) and negative likelihood ratio (LR_) of a rise in ANCA during remission on subsequent relapse of disease were 2.84 (95% CI 1.65, 4.90) and 0.49 (95% CI 0.27, 0.87), respectively. The summary estimates for $LR+$ and LR_ of persistent ANCA during remission for subsequent disease relapse were 1.97 (95% CI 1.43, 2.70) and 0.73 (95% CI 0.50, 1.06), respectively. There was substantial between-study heterogeneity, which was partially explained by the frequency of ANCA measurements.

Conclusion. Among patients with AAV, a rise in or persistence of ANCA during remission is only modestly predictive of future disease relapse. There is limited use to serial ANCA measurements during disease remission to guide treatment decisions for individual patients with AAV.

Key words: vasculitis, anti-neutrophil cytoplasmic antibodies, biomarker



Rheumatology (Oxford). 2012;51:100–109



Rheumatology (Oxford). 2012;51:100–109

Maintenance Induction

Response rates of up to 90%

Relapses are frequent if maintenance therapy is not used (the rate of relapse and time to first relapse varies considerably)

Maintenance immunosuppression for at least

18–24 months : 2 mg/kg daily of azathioprine

None has shown a substantial benefit over AZA

Low dose G.c (6-8 months)

- Continued

The optimal duration of maintenance therapy remains unclear and is currently being investigated in the REMAIN trial

Dialysis dependent patients : 2-3 months

CYCAZAREM trial

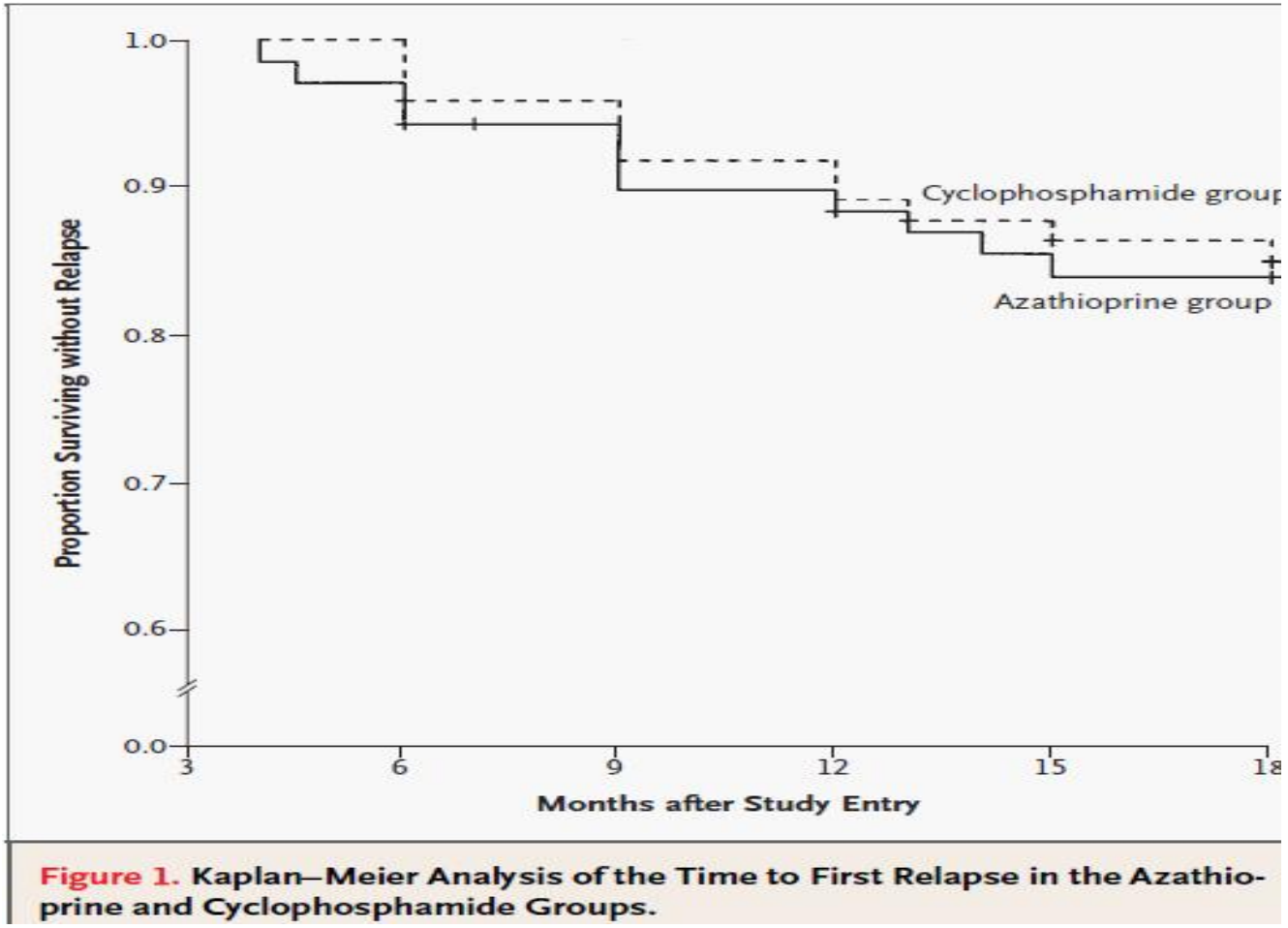


Figure 1. Kaplan–Meier Analysis of the Time to First Relapse in the Azathioprine and Cyclophosphamide Groups.

Relapse in the azathioprine group :15.5 percent [95% CI, 6.9 to 24.0], as did 13.7% in the cyclophosphamide group confidence interval, [CI,5.6 to 21.7]; P=0.65; difference, 1.8 percentage points [95 %CI , –9.9 to 13.0]

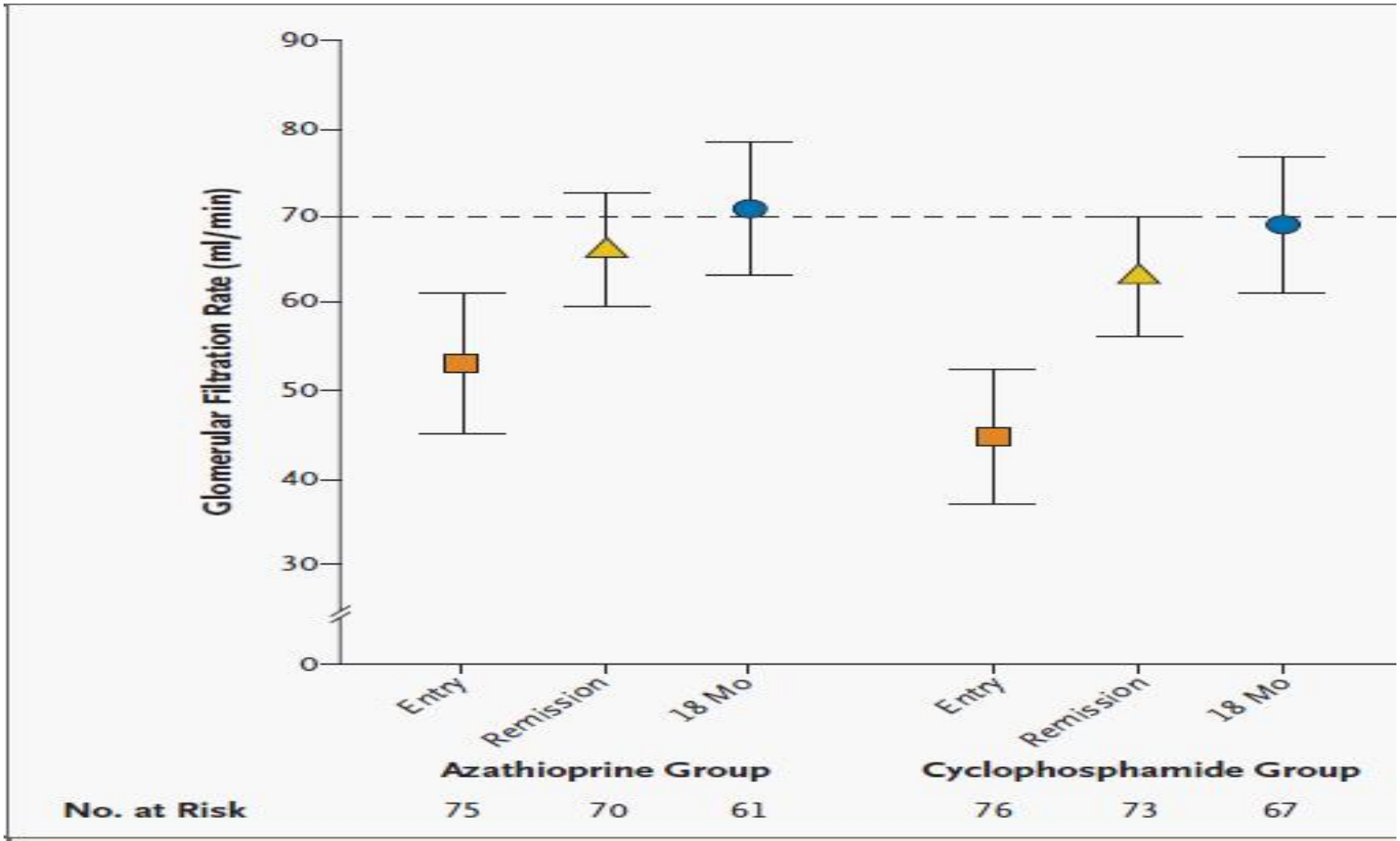
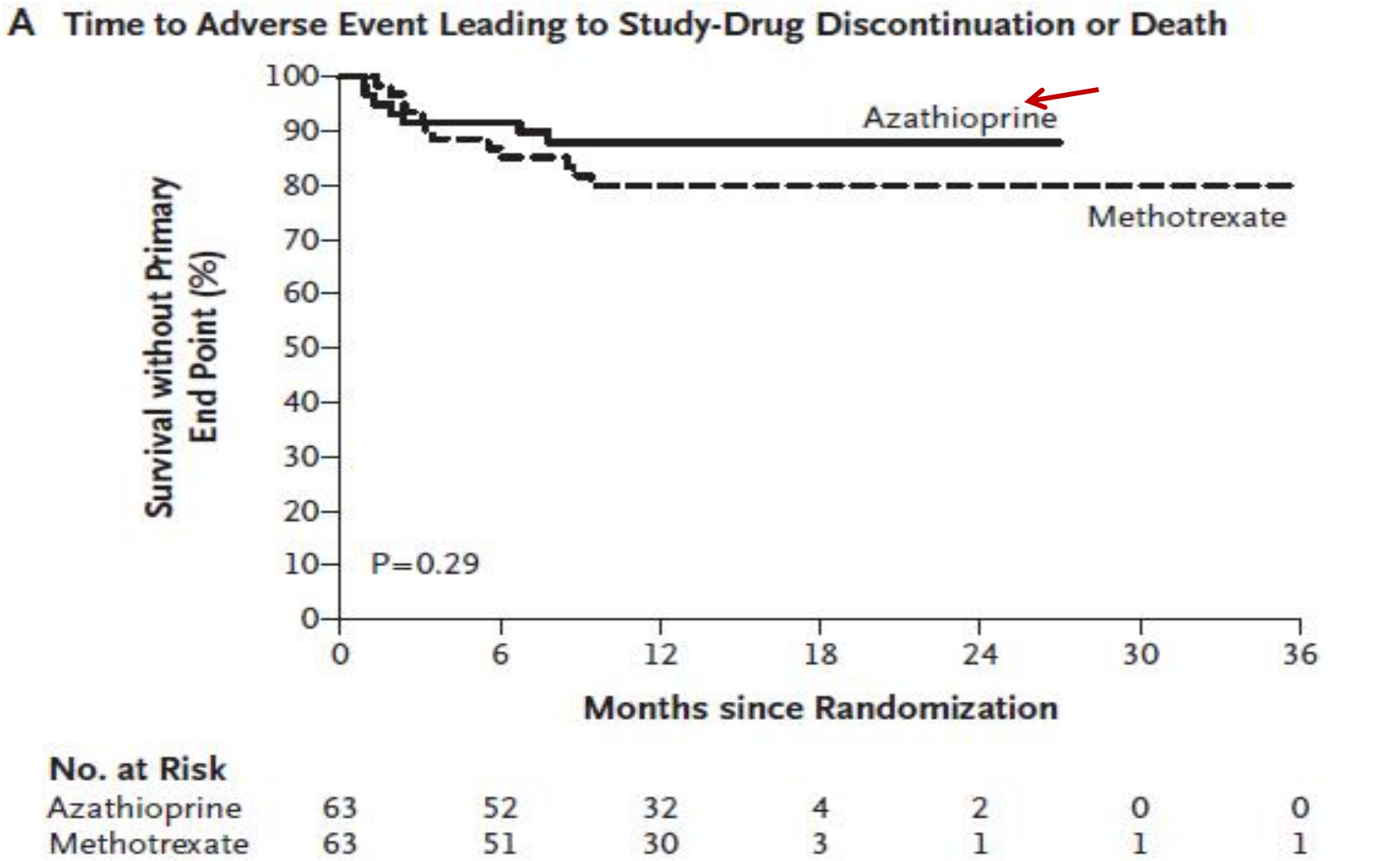


Figure 2. Change in the Glomerular Filtration Rate from Study Entry to the End of the Study (18 Months) in the Azathioprine and Cyclophosphamide Groups.

increase of 17.5 ml /min(95% CI, 11.9 to 23.1) in the Aza group (r2 = 0.57) and an increase of 23.5 ml /min (95%I, 18.2 to 29.0) in the Cyc group (r2 = 0.56)

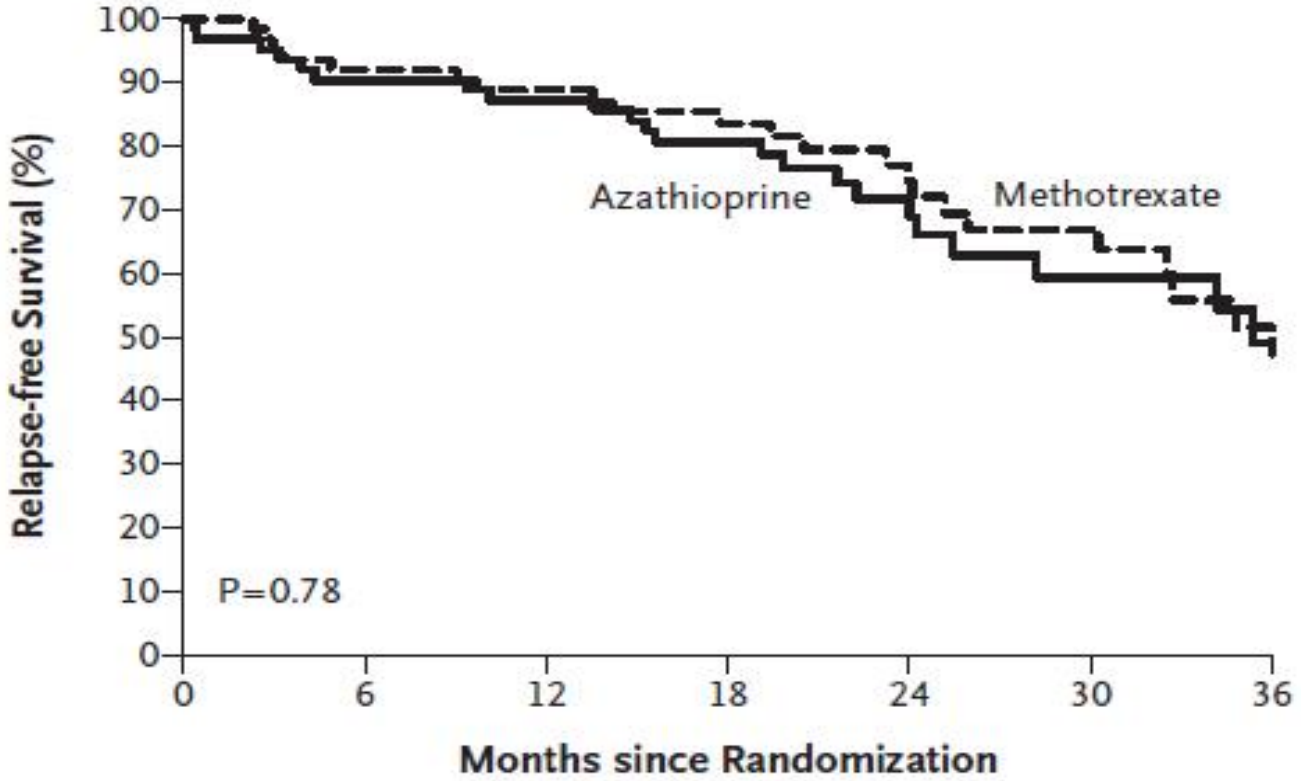
N Engl. J Med 2003;349:36-44

WEGENT trial



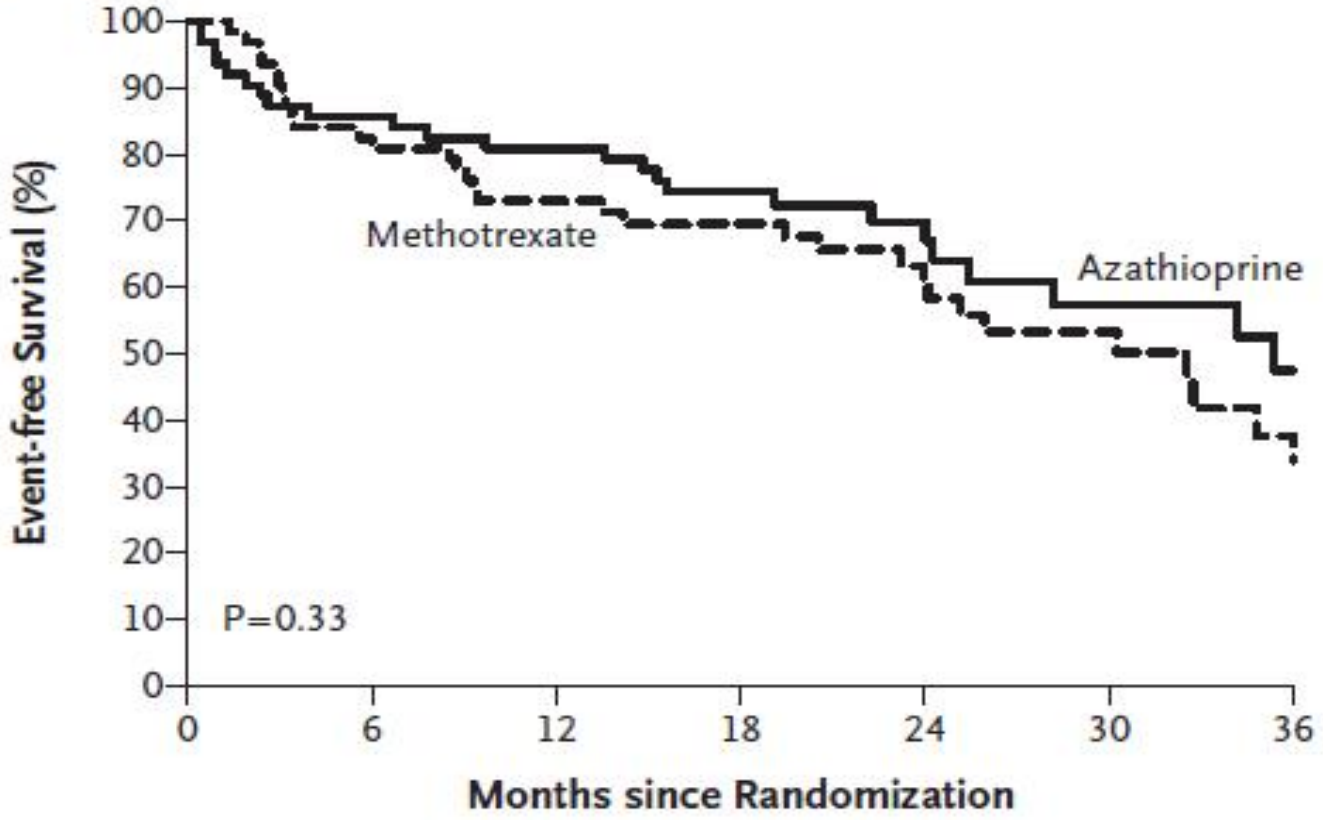
N Engl j Med 359;26 december 25, 2008

B **Time to First Relapse**



No. at Risk							
Azathioprine	63	57	54	43	25	14	9
Methotrexate	63	58	53	44	30	22	11

C Time to First Event



No. at Risk							
Azathioprine	63	54	50	39	24	14	9
Methotrexate	63	53	45	38	25	17	9

IMPROVE trial

MMF was less effective than AZA (unadjusted HR 1.69) in the IMPROVE trial

Relapses were more common in the MMF group but the results showed no significant differences in adverse event rates, estimated GFR or proteinuria.

Second line agent in patients with impaired renal function who are intolerant to AZA and cannot be given MTX.

Table 6 | Randomized controlled trials for maintenance of remission in AAV

Trial (number of patients)	Inclusion criteria	Treatment groups (dose)	Primary end points	Outcome
CYCAZAREM[63] (144)	GPA, MPA or relapse and renal or vital organ involvement	Oral azathioprine (2 mg/kg) versus oral cyclophosphamide (1.5 mg/kg daily)	Relapse Adverse events	No difference in relapse
IMPROVE[65] (165)	New diagnosis of GPA or MPA	Oral mycophenolate mofetil (2 g daily) versus oral azathioprine (2 mg/kg)	Time without relapse Adverse events	More relapses with mycophenolate mofetil than azathioprine, trend towards more adverse events with azathioprine
WEGENT[64] (126)	GPA or MPA and renal or multiorgan involvement	Methotrexate (0.3 mg/kg once weekly) versus azathioprine (2 mg/kg)	Adverse events with consecutive treatment cessation or death	No difference between groups in primary end point and relapses
LEM[67] (54)	Generalized GPA and creatinine <1.3 mg/dl	Leflunomide (30 mg daily) versus methotrexate (up to 20 mg per week)	Relapse	More relapses with methotrexate than leflunomide, trend towards more adverse events with leflunomide
WGET[66] (174)	GPA and BVAS >3	Etanercept and methotrexate or cyclophosphamide versus placebo and methotrexate or cyclophosphamide	Sustained remission for >6 months	No benefit with etanercept, more cancers in etanercept group

Table 5 | Recommendations for maintenance of remission of AAV according to EUVAS disease stage[59]

Disease stage	Treatment	Dose
Localized	Co-trimoxazole	960 mg twice daily
Early systemic	Methotrexate	20–25 mg per week and low-dose glucocorticoids
Early systemic with severe upper respiratory tract involvement	Co-trimoxazole	960 mg twice daily or three times per week
Generalized	Azathioprine	2 mg/kg daily for 12 months, thereafter 1.5 mg/kg daily and low-dose glucocorticoids
Generalized	Methotrexate	20–25 mg per week and low-dose glucocorticoids
Generalized	Leflunomide	20 mg daily and low-dose oral glucocorticoids
Generalized	Rituximab	375 mg/m^2 or 0.5 g or 1 g infusions every 4–6 months

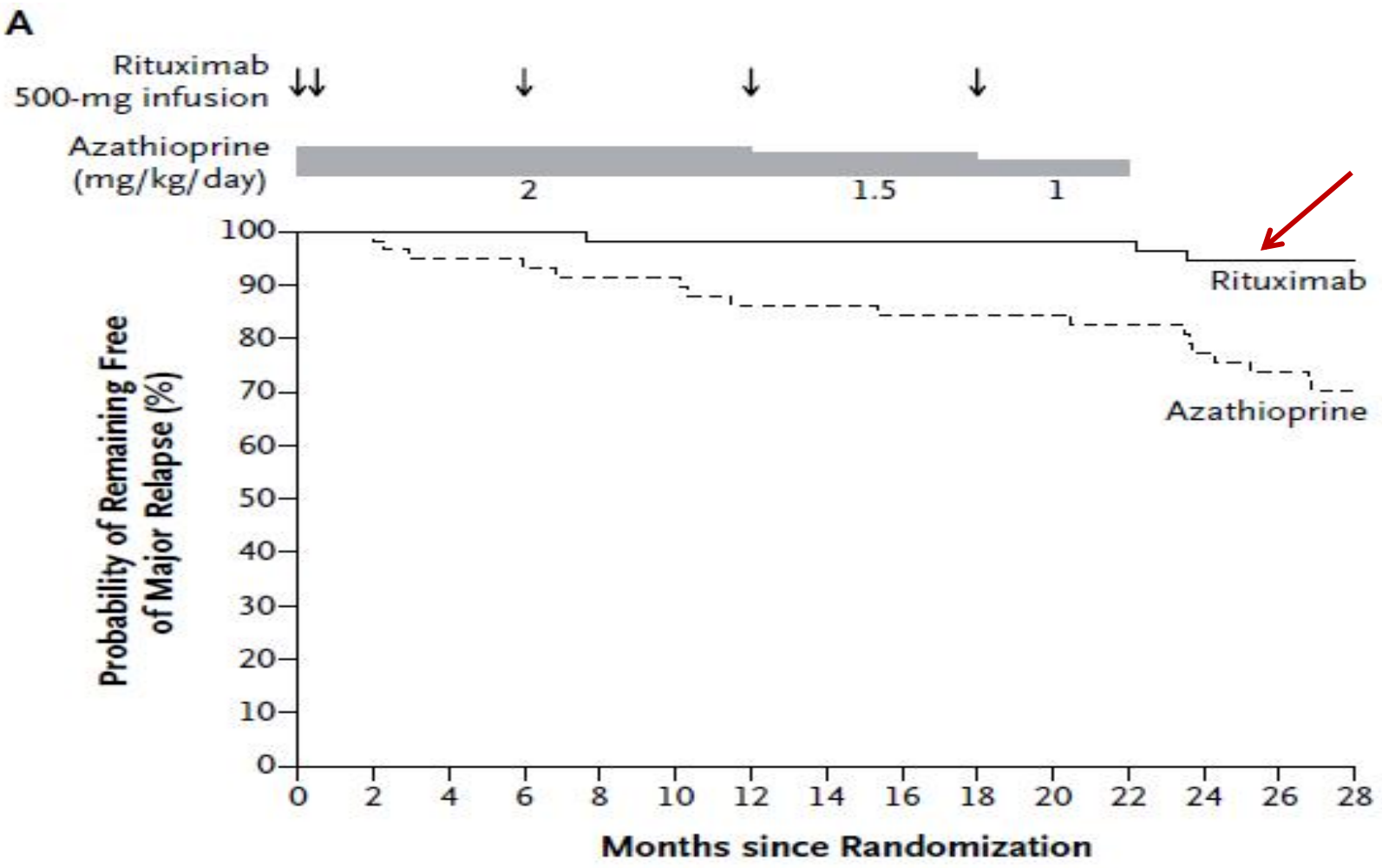
Table 6 Trials of maintenance therapy in AAV in progress or completed and not yet published

Trial	Indication	Induction	Maintenance (trial)	Maintenance (control)	Primary endpoint	Trial number
Maintenance trials						
REMAIN[131]	GPA or MPA patients who remain c-ANCA positive in remission (n=180)	Cyc + Pred	Aza for 48 months	Aza for 18 months	Disease-free survival during 48 months of follow-up	NCT00128895
MAINRITSAN[90]	New or relapsed GPA or MPA within a month of remission (n=117)	Cyc + Pred	Rtx 0.5 mg every 6 months with last dose at month 18	Aza 2 mg/kg tapering from 12 months to zero at 22 months	Number of major relapses (BVAS >10) within 28 months	NCT00748644
RITAZAREM[91]	Relapsing GPA or MPA (n=190)	Rtx + Pred	Rtx 1 g every 4 months for 2 years then monitor for 2 years	Aza for 2 years, then monitor for 2 years	Time to first relapse	NCT01697267
BREVAS[132]	ANCA-positive GPA or MPA in remission treated for active disease in past 26 weeks (n=400)	Cyc + Pred or Rtx + Pred	Belimumab plus Aza 2 mg/kg	Placebo plus Aza 2 mg/kg	Time to first relapse	NCT01663623

MAINRISTAN trial

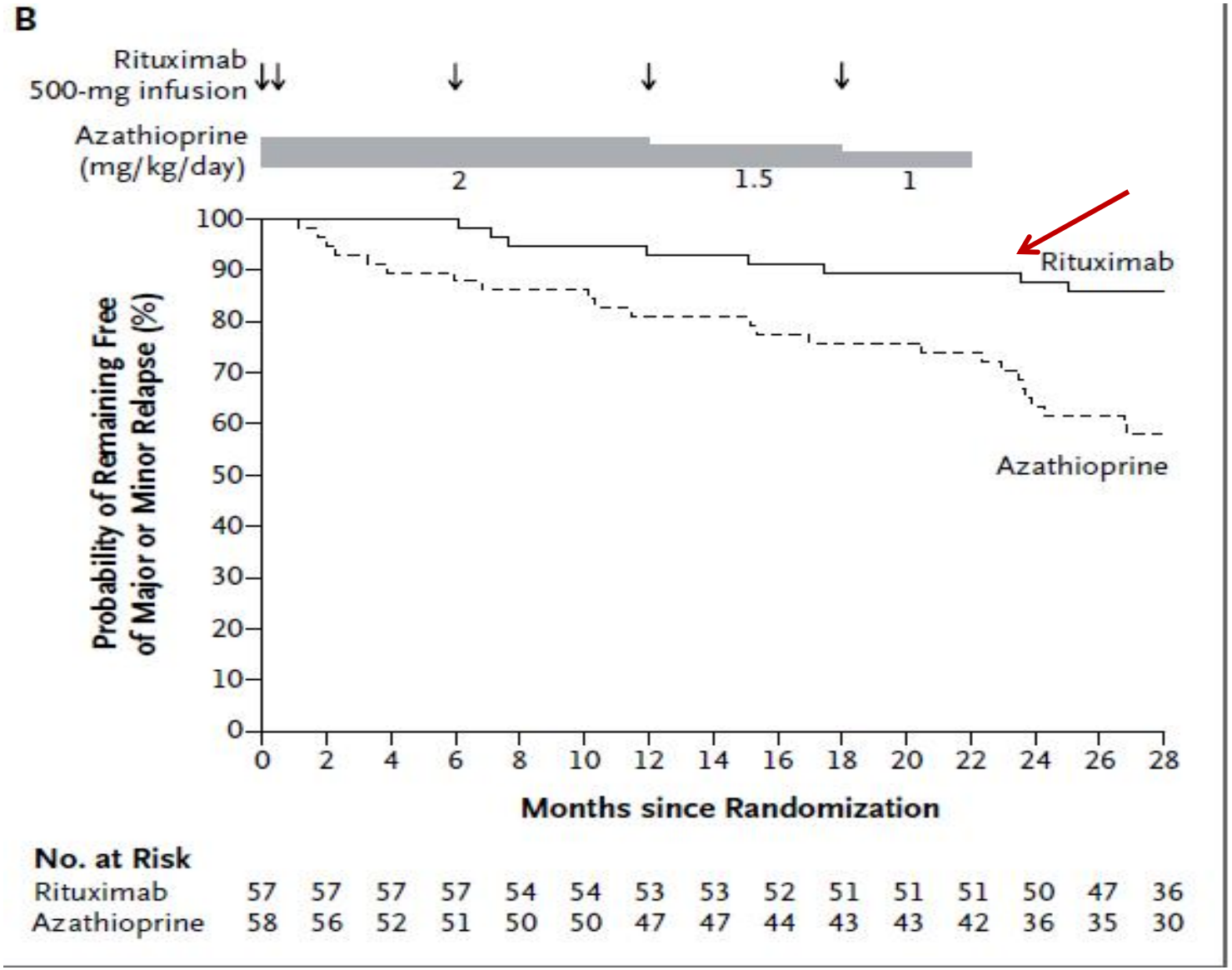
At month 28, major relapse had occurred in 17 patients in the azathioprine group (29%) and in 3 patients in the rituximab group (5%) (hazard ratio, 6.61; 95% CI, 1.56 to 27.96; P = 0.002)

N Engl J Med 2014; 371: 1771-80



No. at Risk

Rituximab	57	57	57	57	56	56	56	56	56	56	56	56	54	52	39
Azathioprine	58	58	55	54	53	53	50	50	48	48	48	47	44	41	33



Hazard ratio: 3.53

Treatment of specific subgroups

Age >60 years: are MPO- ANCA- positive

advanced age and severely impaired renal function are predictors of high mortality from infections within the first year of treatment

less-intensive immunosuppressive therapy

Localized GPA (limited to the upper respiratory tract) : co-trimoxazole alone or in combination with glucocorticoids

Refractory to Treatment

Is low(4-5%)

1-Unchanged or increased disease activity in acute stage after 4 weeks of treatment

2-No response after 4–6 weeks of treatment

3-Chronic, persistent disease with presence of at least one major or three minor items

4-Intolerance of, or contraindications to, cyclophosphamide and glucocorticoids

EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Study Group

Refractory

Riutximab: 375mg/m2,once a week (response rate of 85% : complete remission : 60%, partial response : 25%)

Intravenous immunoglobulin: 2gr/kg or 0.4 gr/kg/d for 4 days especially in Patients with infection

Mychophenolate mofetile: 2 gr daily

15-Deoxyspergualin: o.5 mg/kg daily for 6 cycles

Infliximab: 3-5 mg/kg infusions once or twice monthly

Antithymocyte globulin: 2.5 mg/kg daily for 10 days (IV)

Alemtuzumab :15 mg on day 1 and 2 at 0 and 6 months

Holle, J. U. *et al. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann. Rheum. Dis. 71, 327–333 (2012).*

Table 4 Trials of induction therapy in AAV in progress or completed and not yet published

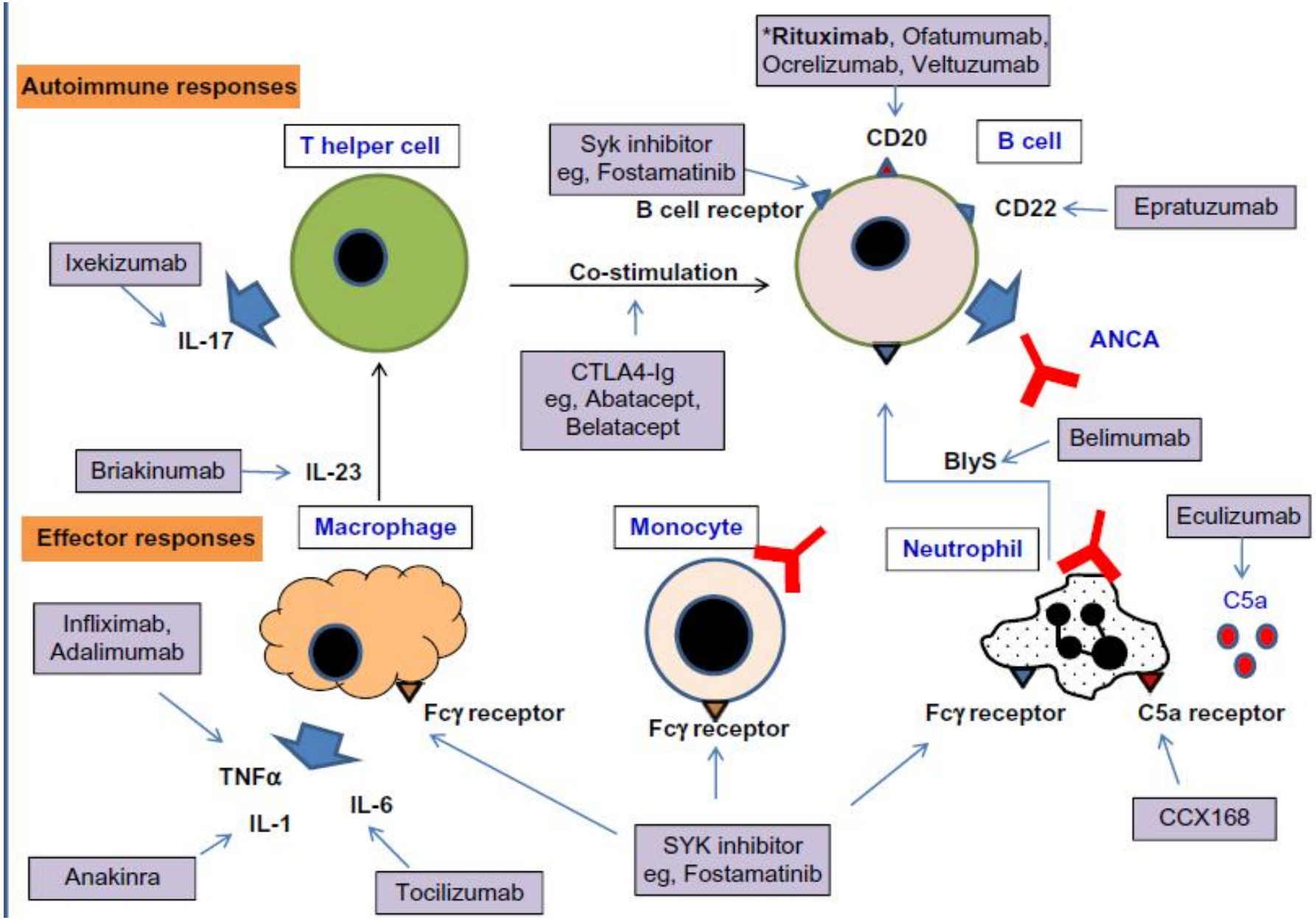
Trial	Indication (total projected n)	Induction (trial)	Induction (control)	Primary endpoint	Trial number
Induction trials					
MYCYC[61]	New onset GPA or MPA (n=140)	MMF and Pred (n=70)	IV Cyc and Pred (n=70)	Remission at 6 months	NCT00414128
PEXIVAS[66]	Renal MPA or GPA (GFR <60 mL per minute) or pulmonary hemorrhage (n=500)	Plex + standard or reduced Pred + Cyc or Rtx (n=250)	Plex + standard or reduced Pred + Cyc or Rtx (n=250)	Composite of all-cause mortality and ESRD	NCT00987389
CLEAR[67]	Renal GPA or MPA (GFR >25mL per minute, n=60)	CCX168 + Cyc + half dose or no Pred	Cyc + standard Pred	Safety of CCX168 (secondary corticosteroid use)	NCT01363388
SPARROW[130]	Relapsed GPA (n=216)	Gusperimus and Pred	Cyc and Pred or rituximab and Pred or MTX and Pred	Proportion of patients in complete or partial remission	NCT01446211
ALEVIATE[118]	Refractory GPA or MPA (n=24)	Alemtuzumab 30 mg on day 1 and 2 at 0 and 6 months (high dose)	Alemtuzumab 15 mg on day 1 and 2 at 0 and 6 months (low dose)	Proportion of patients in complete or partial remission	NCT01405807

New and emerging therapies

B-cell therapies

T-cell-directed therapies

Cytokine therapies


Autoimmune responses
*Rituximab, Ofatumumab, Ocrelizumab, Veltuzumab
CD20
B cell
T helper cell
Syk inhibitor eg, Fostamatinib
B cell receptor
CD22
Epratuzumab
Ixekizumab
IL-17
Co-stimulation
CTLA4-Ig eg, Abatacept, Belatacept
ANCA
Belimumab
BlyS
Briakinumab
IL-23
Macrophage
Effector responses
Monocyte
Neutrophil
Eculizumab
C5a
Infliximab, Adalimumab
Fcγ receptor
Fcγ receptor
Fcγ receptor
C5a receptor
TNFα
IL-6
IL-1
Anakinra
Tocilizumab
SYK inhibitor eg, Fostamatinib
CCX168

B-cell therapies

Rituximab: Anti-CD20 chimeric monoclonal antibody

Belimumab : fully humanized monoclonal antibody to soluble BlyS

Epratuzumab : Anti-CD22 monoclonal antibody

T-cell-directed therapies

Antithymocyte globulin

Anti-CD52 antibodies : alemtuzumab

Abatacept : soluble, therapeutic CTlA4–Ig, can prevent delivery of the second co-stimulatory signal that is required for the optimal activa tion of T cells, by blocking the engagement of CD28

Cytokine therapies

Etanercept : a recombinant,soluble, human, TNF receptor fusion protein

Inflix imab: a chimeric anti-TNF monoclonal ab

Tocilizumab: a fully humanized monoclonal ab directed against the Il-6 receptor

selective Syk inhibitor

Inhibition of Ras : Ras family of GTPases, cell signaling molecules that act downstream of tyrosine kinase.

Table 1 EBMT database of autoimmune diseases, June 2011

Diseases	*No. of patients*		
	Paediatrics[a] *Auto/Allo*	*Adults Auto/Allo*	*Total Auto/Allo*
Neurological diseases	9/0	493/4	502/4
Multiple sclerosis	7/0	462/3	469/3
Other neurological diseases, for example, myasthenia gravis	2/0	31/1	33/1
Connective tissue diseases	29/1	367/1	396/2
Systemic sclerosis	9/0	257/0	266/0
Systemic lupus erythematosus	17/1	78/1	95/2
Polymyositis–dermatomyositis	0	16/0	16/0
Other connective tissue disease, including Sjogren's disease	2/0	16/0	18/0
Arthritis	62/4	90/2	152/6
Rheumatoid arthritis	1/0	75/2	76/2
Juvenile chronic arthritis	61/3	10/0	71/3
Other arthritis, including psoriatic	0/1	5/0	5/1
Vasculitis	3/3	26/1	29/4

new therapeutic perspectives

1-Targeting the CX3CL1/CX3CR1 pathway

2- Blocking IL-23 production and/or subsequent recruitment of IL-17A-gamma-delta T cells producing effector and CD3 CD4 CD8 gamma-delta T cell receptor NK1.1 T cells of glomerular cells

Relapse

Occurrence of increased disease activity after a period of partial or complete remission.

Worsening of pre-existing disease activity or the recurrence or development of active GN

New signs or symptoms of vasculitis in any organ system

safe dose of cyclophosphamide?

Relapse

PR3-ANCA positivity(GPA)

Suboptimal intensity of induction therapy

Persistence of ANCA after induction of remission or a rise in ANCA titres

chronic nasal carriage of *S. aureu*

Patients with granulomatous disease of the upper airways

Reliable markers to predict relapse

- CD8 T cell messenger RNA signature
- Calprotectin (S100A8/S100A9) is a damage associated molecular pattern produced by neutrophils and monocytes
- Urinary monocyte chemoattractant protein 1
- RAVE study : the absence of both B cells and ANCAs after treatment was associated with a low risk of relapse

-Continued

Mild relapses during maintenance therapy: temporary increase of the glucocorticoid dose (to 0.5 mg/kg of body weight)

Relapse after maintenance therapy period: repeat the same drugs

Severe renal involvment: Rituximab seems to be superior to cyclophosphamide in the treatment of relapsing disease (RAVE trial)

Antiglomerular basement membrane (GBM) disease

Is rare

Lung haemorrhage

Anti-GBM antibody [α3(IV)NC1]

ANCAs(in elderly and those who have lower proteinuria or systemic involvement

Plasmapheresis, corticosteroids, and Cyclophosphamide

Plasmapheresis

Single plasma exchange removes ~70% of IgG, with a sustained reduction in antibody

levels usually achieved after approximately five exchanges

One 4-liter exchange per day with 5% albumin. Add 150–300 ml FFP at the end of each pheresis session in pulmonary hemorrhage

Ann Intern Med 2001;134:1033–42.

Treatment

Methylprednisolon: 15-30 mg/kg

Cyclophosphamide: 2-3 mg/kg for 3 months

Dialysis dependent patients

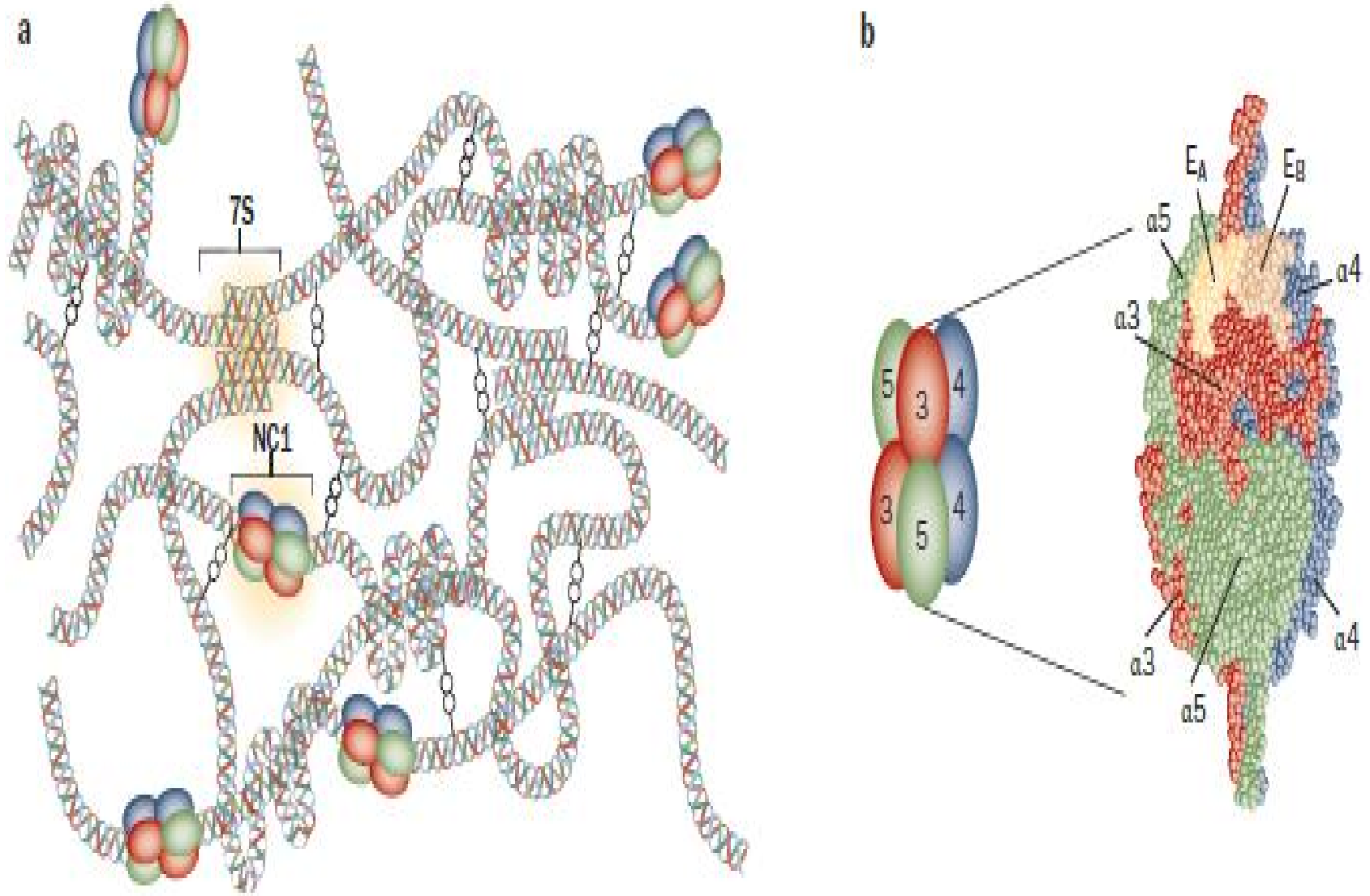
Mild renal dysfunction

Table 31 | Therapy of anti-GBM GN

Corticosteroids	
Week	**Prednisone dose**
0–2	Methylprednisolone 500–1000 mg/d i.v. for 3 days, followed by prednisone, 1 mg/kg/d IBW (maximum 80 mg/d)
2–4	0.6 mg/kg/d
4–8	0.4 mg/kg/d
8–10	30 mg/d
10–11	25 mg/d
11–12	20 mg/d
12–13	17.5 mg/d
13–14	15 mg/d
14–15	12.5 mg/d
15–16	10 mg/d
16–	IBW <70 kg: 7.5 mg/d IBW ≥ 70 kg: 10 mg/d
Discontinue after 6 months	

Combined therapy has an overall beneficial effect on overall survival (HR 0.31, 95% CI 0.15–0.63, *P = 0.001) and renal survival (HR 0.60, 95% CI 0.37–0.96, P = 0.032).*

Nat. Rev. Nephrol. 7, 697–705 (2011)


a
7S
NC1
b
5
3
4
3
5
4
E_A
E_B
a5
a4
a3
a3
a5
a4

Rituximab

Rituximab with prednisone may be an alternative treatment option for anti-GBM antibody disease. (A case-based review)

Controlled studies need.

Semin Arthritis Rheum 42:567–572 , 2013

Maintenance Therapy

1-Low-dose C.s and Azt :six to nine months

2-Approximately three months of Cyclo and C.s and C.s alone for the subsequent six to nine months

3-If anti-GBM antibody titers are persistentl negative → 2-3months

predictors of kidney survival in anti-GBM GN

SCr at presentation

The need for dialysis at presentation

Percentage of glomerular crescents

Prognosis

The rarity and the fulminant course of anti-GBM disease:

Johnson, J. P. *et al Medicine (Baltimore) 64, 219–227 (1985).*

Scr level at presentation is an independent predictor of renal failure (HR 2.07, 95% CI 1.61–2.65, *P <0.001).*

a large cohort study from a single center. *Medicine (Baltimore) (in press)*

-Continued

Survival of 70-80% at 1 year

Titer of anti-GBM antibodies(HR:1.16, 95% CI 1.04–1.30, *P = 0.009)*

Coexistence of ANCA in serum *(HR 2.18, 95% CI 1.09–4.38, P = 0.028)*

Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Ann. Intern. Med. 134, 1033–1042 (2001).*

Conclusion

Multidisciplinary approach

A timely diagnosis

Treat the disease

Prevent relapse

Manage long-term cardiovascular risk, organ damage, and side effects of therapy.