Management of pulmonary-renal syndromes due to vasculitis

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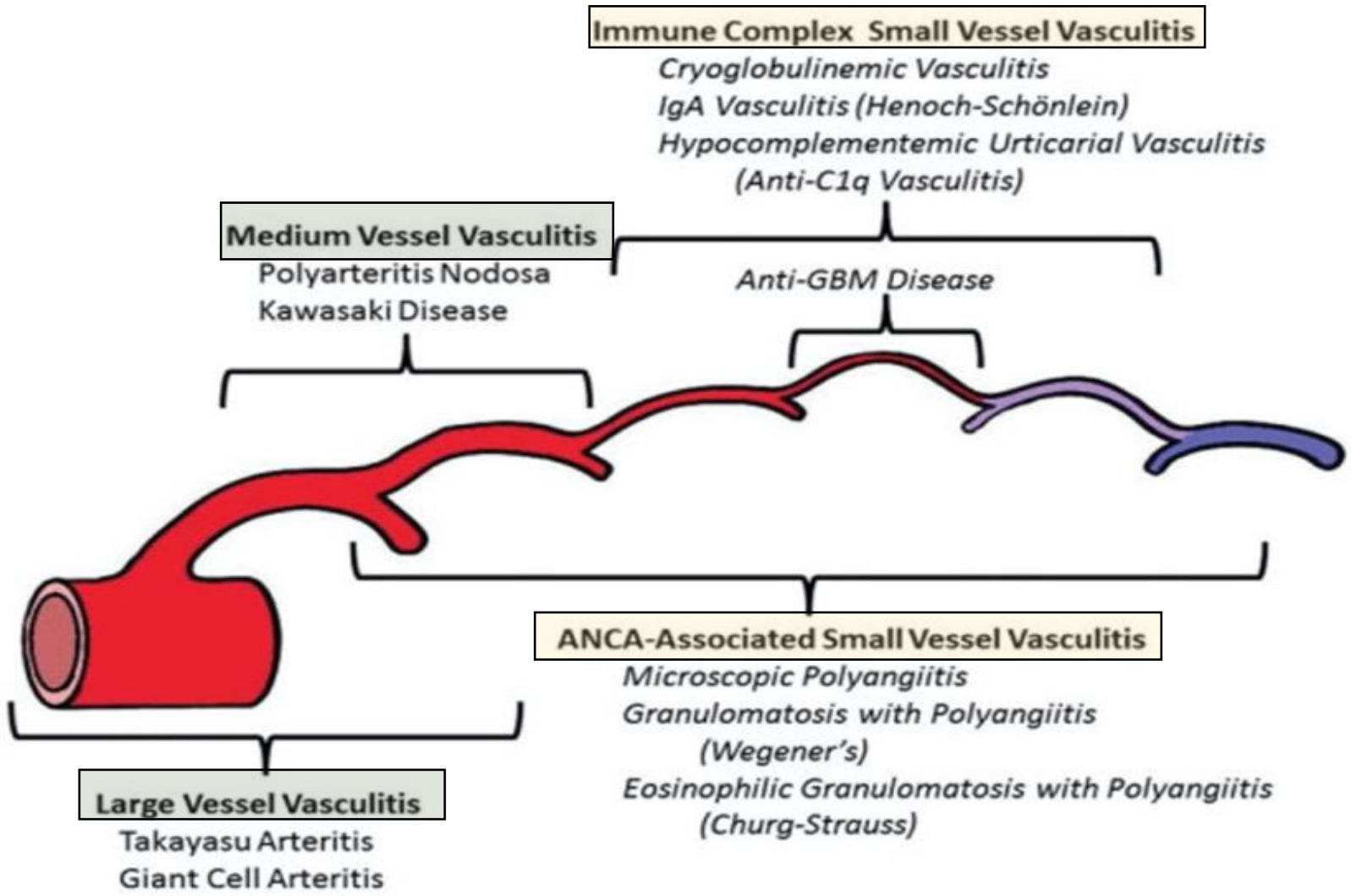
Introduction

- Vasculitis is defined by an inflammatory damage to the vessel walls resulting to the development of serious and often fatal condition. .

- Existence of a wide clinical spectrum associated with overlaps in the presentation of vasculitides adds significant challenges to the management of these complex disorders.



Classification of vasculitides Based on 2012 International Chapel Hill Consensus Conference

ANCA-associated vasculitis (AAV)

	5-year- survival
• **GPA:** Granulomatosis with polyangeiitis	74-91%
• **MPA:** Microscopic Polyangeiitis	45-76%
• **EGPA:** Eosinophilic granulomatosis with polyangiitis	60-97%

The mortality of AAV approached 93% within 2 years prior to effective therapy.
The introduction of glucocorticoids in 1948 and cyclophosphamide in 1960s along with other therapies like antihypertensive medications and renal replacement therapy has transformed the survival.

Treatment goals of AAV

Remission induction

- Induction of remission
- Reduction of morbidity and mortality
- Minimizing of the drug induced toxicity

Maintenance therapy

- Control of the disease activity
- Prevention of the disease relapse
- Minimization of the drug-induced toxicity

Case Presentation

A 52-year-old man with nasal discharge and sinusitis for 6 months was admitted to the hospital with massive hemoptysis. There was a history of progressive weight loss and weakness over 3 months. Serum creatinine was 6 mg/dl, and the PR3 ANCA was positive. The results of kidney biopsy revealed a diagnosis of pauci-immune crescentic GN.

Question 1: Based on the current data what immunosuppressive regimen can be recommended as induction therapy for this patient?

Organ/life-threatening manifestations of GPA and MPA

- Active glomerulonephritis
- Pulmonary hemorrhage
- Cerebral vasculitis
- Progressive peripheral or cranial neuropathy
- Orbital pseudo-tumor
- Scleritis
- Gastrointestinal bleeding due to vasculitis
- Cardiac disease due to vasculitis (pericarditis, myocarditis)

Non-Organ/life-threatening manifestations of GPA and MPA

- Rhinosinusitis
- Arthritis
- Pulmonary nodules

Guidelines in the management of ANCA-associated vasculitis are presented by the following societies

British Society of Rheumatology/
British Health Professionals in Rheumatology

European league against Rheumatism/
European Renal Association-
European Dialysis and Transplant Association

Canadian Vasculitis Society

Brazilian Society of Rheumatology

Society	Publication year	Stake holders	Geography
BSR/BHPR	2014	Vasculitis physician experts from multiple specialties and allied health care professional representatives	United Kingdom
EULAR/ERA-EDTA	2015	International task force representing EULAR, ERA, and EUVAS, and including physicians (internists, specialists, and pathologists), patients, nurses	Europe
CanVasc	2016	Vasculitis physician experts from multiple specialties	Canada
SBR	2017	Rheumatologists	Brazil

Geetha D., et al. Kidney International Reports 2018; 3:1039-49

Glucocorticoids as induction therapy for AAV

- Glucocorticoids has a central role in management of AAV, but are insufficient by themselves.
- Patients with RPGN or pulmonary hemorrhage typically receive intravenous pulse of methylprednisolone followed by high dose oral prednisolone.
- Prednisolone is tapered to 5-10 mg/d at 6 months; however, there is no consensus about the best tapering regimen or the duration of glucocorticoid therapy.

The NEW ENGLAND JOURNAL of MEDICINE

PEXIVAS Trial

ORIGINAL ARTICLE

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

Patients with severe ANCA associated vasculitis (GFR<50 c/min or pulmonary hemorrhage)

1 to 3 g of IV methylprednisolone over 1 to 3 days

Oral prednisolone or prednisone

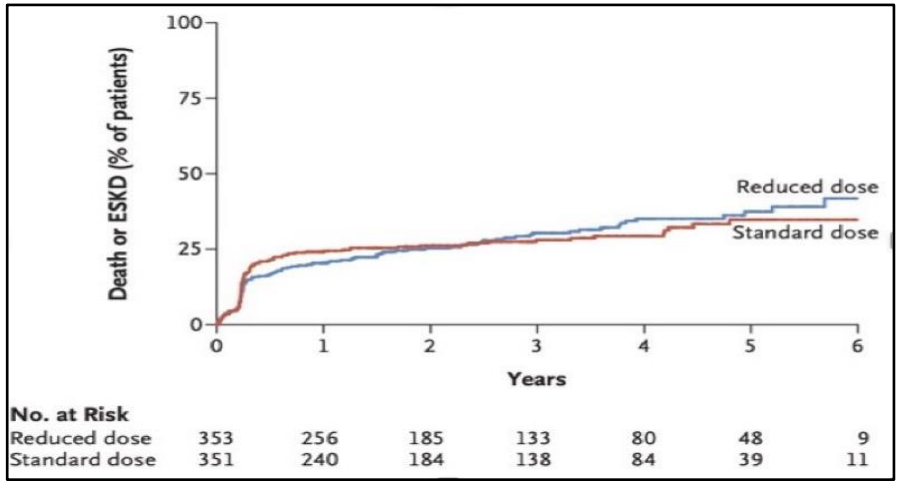
Standard-dose group:
Tapered from 1mg/kg/d to 5 mg/d over 6 months
Slow de-escalation schedule

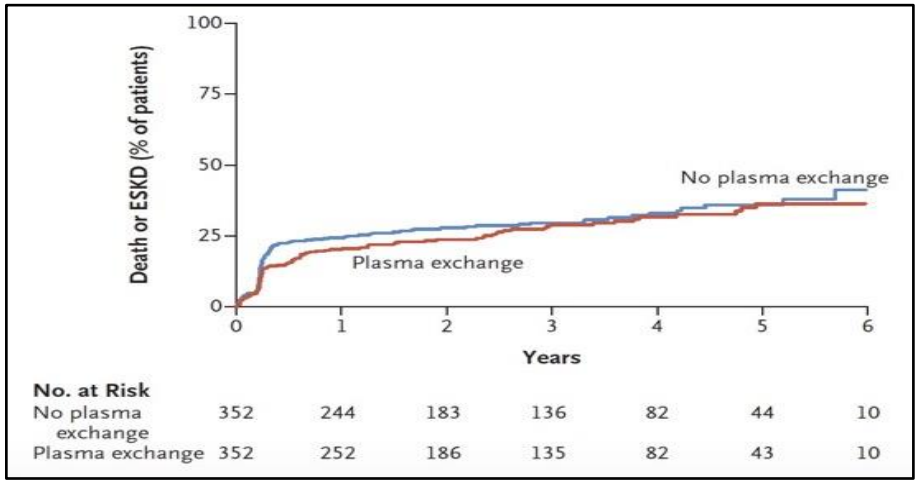
Reduced-dose group:
Tapered from 1mg/kg/d to 5 mg/d over 6 months
rapid de-escalation schedule

Week	Standard			Reduced-dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	pulse	pulse	pulse	pulse	pulse	pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12.5	15	20
9-10	20	25	30	10	12.5	15
11-12	15	20	25	7.5	10	12.5
13-14	12.5	15	20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10	15	5	5	7.5
19-20	7.5	7.5	10	5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' Local Practice			Investigators' Local Practice		

Walsh M., et al. N Engl J Med 2020; 382:7

PEXIVAS Trial





Secondary Outcome	Plasma Exchange vs. No Plasma Exchange	Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen
	effect size (95% CI)	
Death from any cause	0.87 (0.58–1.29)	0.78 (0.53–1.17)
End-stage kidney disease	0.81 (0.57–1.13)	0.96 (0.68–1.34)
Sustained remission	1.01 (0.89–1.15)	1.04 (0.92–1.19)
Serious adverse events	1.21 (0.96–1.52)	0.95 (0.75–1.20)
Serious infections at 1 year	1.16 (0.87–1.56)	0.69 (0.52–0.93)

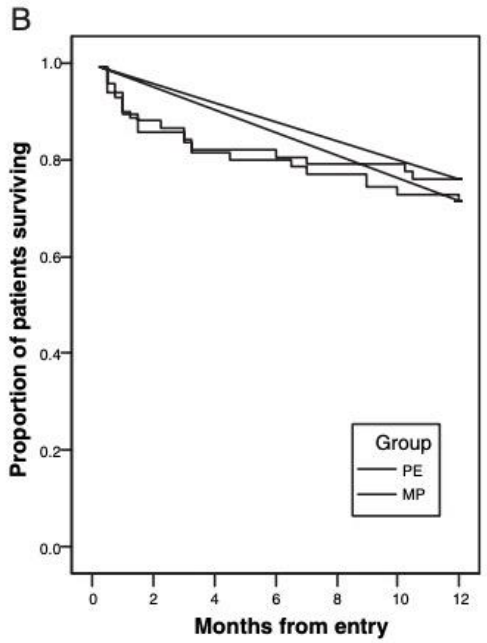
- **The rates of death and ESKD were similar in patients on standard and reduced dose regimen of glucocorticoids.**
- **Serious infections at one year were less common in the reduced-dose group than in the standard dose group.**
- **Plasma exchange did not reduce the rate of death or ESKD in patients with severe ANCA-associated vasculitis..**

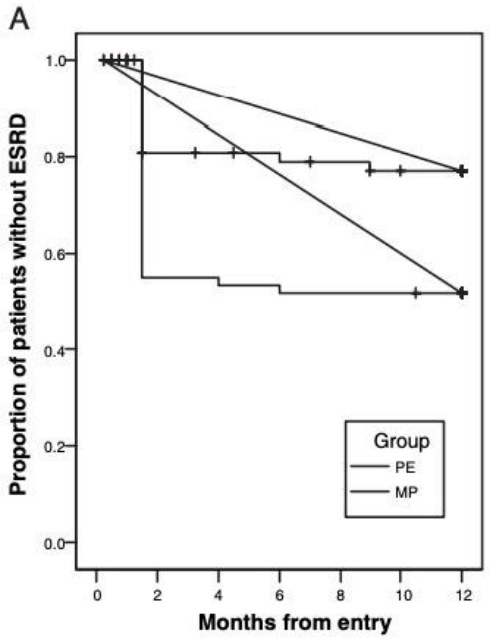
Walsh M., et al. N Engl J Med 2020; 382:7

IV Methylprednisolone vs plasma exchange (MEPEX trial)

- In 137 patients with GPA or MPA and a serum Cr of above 5.7 mg/dl (500 µmol/L), plasma exchange reduced the risk of ESKD at one year in ANCA associated vasculitis compared with IV methylprednisolone.

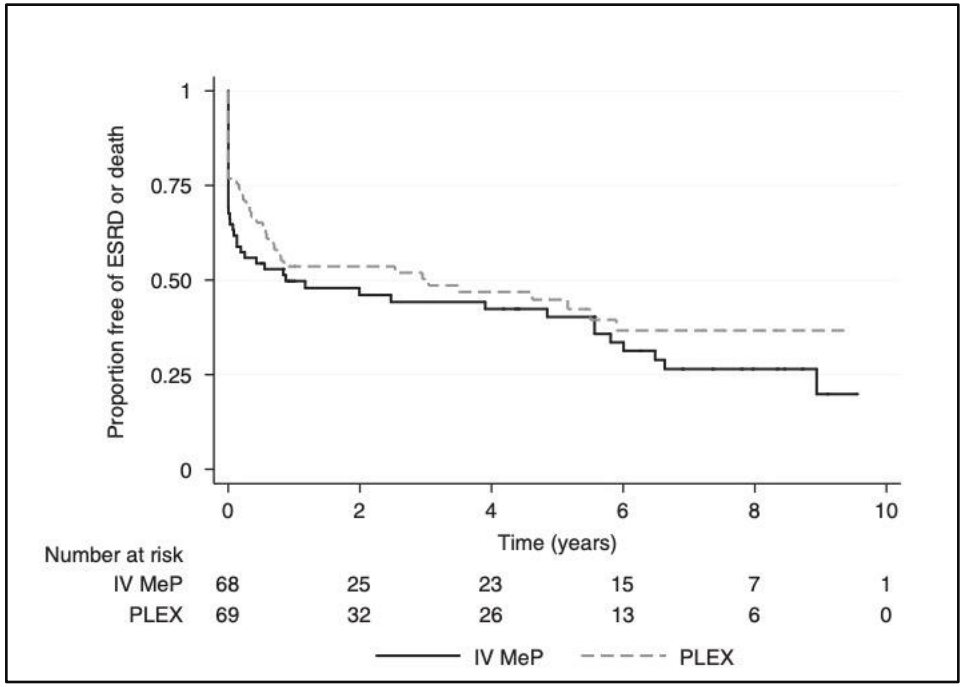
- Patients survival was similar in both groups.





Jayne R.W.,et al. J Am Soc Nephrol 2007; 18:2180-88

- **Long term follow up of patients from the MEPEX trial did not show improved outcome with plasma exchange.**
- **The long term benefits of plasma exchange in ANCA positive vasculitis remains unclear.**



Walsh M., et al. Kidney Int 2013; 84: 397-402

Indications of plasma exchange in GPA and MPA

- Patients who are positive for anti-GBM
- Patients with pulmonary hemorrhage?
- Patients with severe kidney disease (Cr> 5.7 mg/dL, dialysis requirement)?

	Disease manifestation	Common view	Differences
Plasmapheresis	Rapidly progressive glomerulonephritis		CanVasc states there is insufficient evidence to recommend plasmapheresis for patients with severe renal or pulmonary involvement, but it may be a reasonable adjuvant if a patient is refractory to high dose GC + CYC/RTX. BSR, SBR, and EULAR recommend consideration of plasma exchange for RPGN with serum Cr greater than ~500 µmol/l (5.7 mg/dl).
Plasmapheresis	Diffuse alveolar hemorrhage	There is insufficient evidence, but may be considered/possibly of benefit as an adjuvant when patients are in this setting and refractory to standard GC + CYC/RTX (all 4 guidelines)	

Intravenous vs. oral cyclophosphamide in management of GPA and MPA

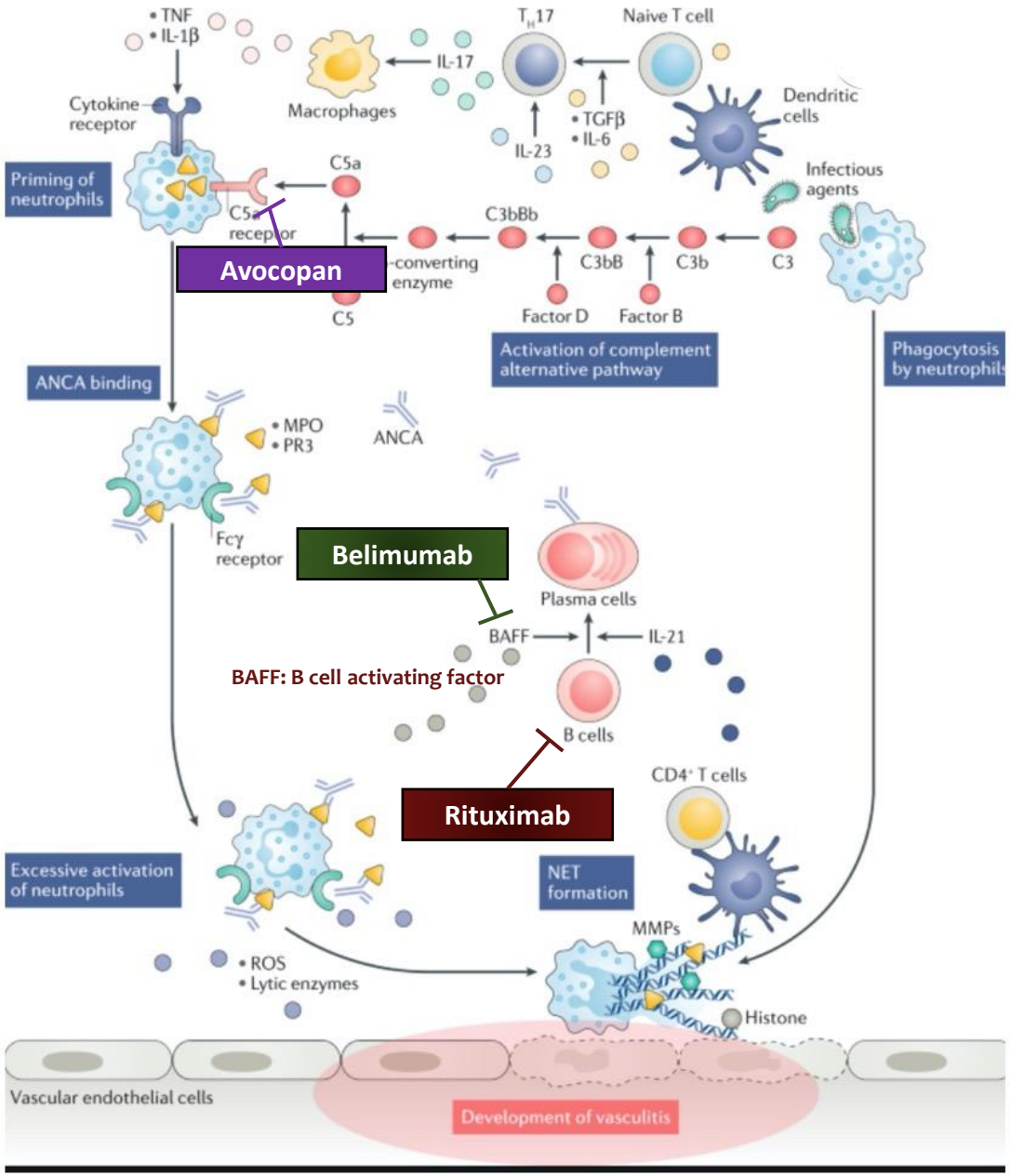
The results of CYCLOPS trial (42 centers in 12 European countries):

- **Intravenous cyclophosphamide was as effective as oral treatment with less treatment related leukopenia.**

Groot K., et al. Ann Intern Med 2009; 150(10)670-80

- **A long term follow up of CYCLOPS trial showed that there was a higher rate of relapse with pulse IV cyclophosphamide than oral formulation, but this did not significantly affect mortality.**

Harper H., et al. Ann Rheum Dis 2012; 71 (6) 955-60



Nakazava D., et al. Nature Reviews Rheumatology 2019; 15: 91-101

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

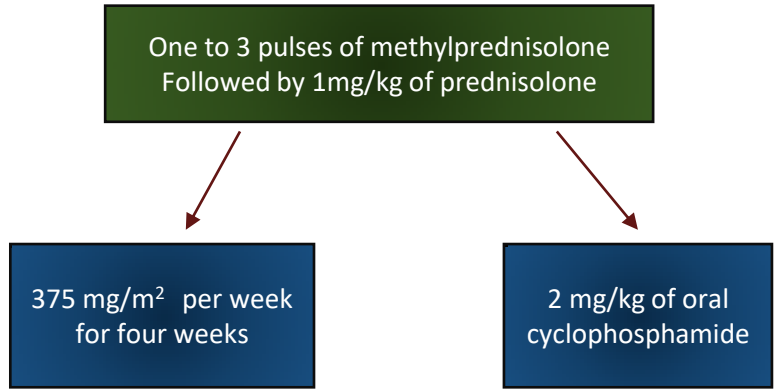
Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

RAVE Trial

Results:

- **At six months, the remission rates of patients treated with rituximab and cyclophosphamide were similar.**
- **Moreover, there was no differences in the rates of adverse effects between two groups.**
- **In patients with relapsing disease, rituximab was superior to cyclophosphamide in induction of remission.**

Participants: 197 patients with new or relapsing ANCA-associated vasculitis
Serum Cr <4 mg/dL

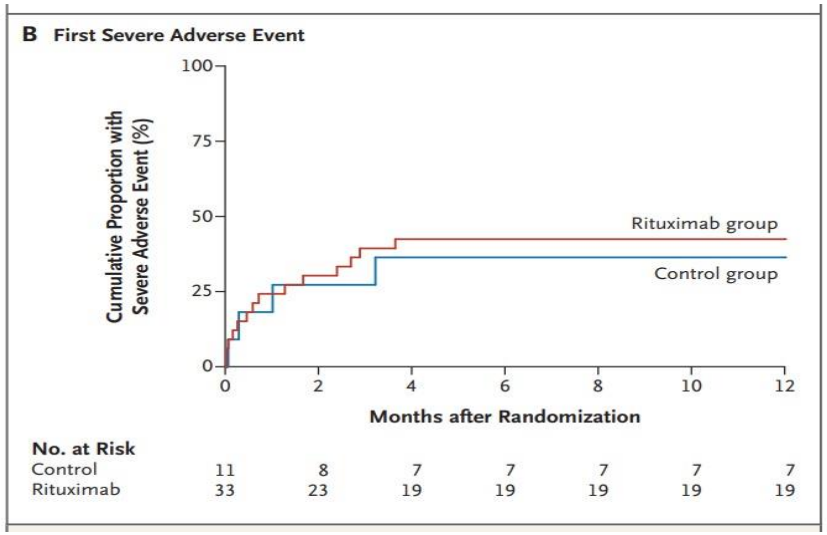


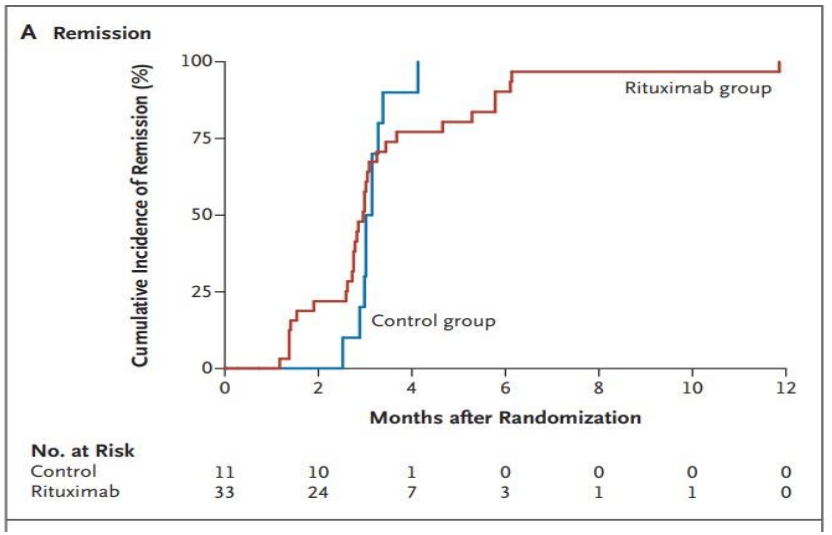
Stone JH., et al. N Engl J Med 2010; 363: 221-232

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

RITUXVAS Trial





- **The trial enrolled only patients with newly diagnosed GPA/MRA with more severe kidney disease than RAVE trial.**
- **The rituximab arm also received 2 to 3 doses of cyclophosphamide.**

Jones RB., et al. N Engl J Med 2010; 363:211-220

Treatment response among patients with PR3 ANCA associated vasculitis received RTX vs. patients with PR3 ANCA associated vasculitis who received Cyclophosphamide-Azathioprine

A post-hoc analysis of the RAVE trial

	OR[1]	95% CI	P-value
All patients with PR3-AAV (n = 131) [2]			
CR at 6 months	2.11	1.04 – 4.30	0.04
CR at 12 months	1.96	0.95 – 4.05	0.07
CR at 18 months	1.44	0.68 – 3.05	0.34
Patients with PR3-AAV with relapsing disease at baseline (n = 81)[3]			
CR at 6 months	3.57	1.43 – 8.93	<0.01
CR at 12 months	4.32	1.53 – 12.15	<0.01
CR at 18 months	3.06	1.05 – 8.97	0.04

1

CR: complete remission, OR: odds ratio, CI: confident interval

No association was found between the kind of treatment and the remission in the patients who were MPO-ANCA positive

Unizony S., et al. Ann Rheum Dis 2016; 75(6): 1166-1169

Rituximab as induction therapy for ANCA-associated vasculitis

- In April 2011 rituximab was approved by the US FDA as an alternative to cyclophosphamide in combination with glucocorticoids in patients with severe GPA/MPA.
- Some authors choose Rituximab-based regimen because of its comparable efficacy and less side effects.
- Others prefer cyclophosphamide-based regimen particularly in patients with more severe kidney disease and/or pulmonary hemorrhage.
- Rituximab is preferred therapy in patients with relapsing and refractory disease and those with concern about fertility, alopecia and malignancy.
- Based on the results of RAVE trial rituximab may be superior to cyclophosphamide in patients with PR3 positive ANCA.

Induction therapy of patients with Non-Organ/life-threatening manifestation of GPA and MPA

- Initial therapy with lower dose of glucocorticoids (0.5 mg/kg/d) combined with weekly oral methotrexate (20-25 mg/kg per week orally) can be suggested.
- Rituximab or mycophenolate can be suggested as alternative initial therapies.
- It seems that the time to remission and the relapse rate in patients who receive methotrexate is higher than those receiving cyclophosphamide.

Induction therapy in patients with severe ANCA-associated vasculitis

Glucocorticoids

IV Methylprednisolone: 7-15 mg/kg
maximum: 500-1000 mg

↓

1-3 days

Oral Prednisolone: 1 mg/kg
Maximum: 60-80 mg/d

↓

1-2 weeks
In patients without
resistance and relapse

Reducing Prednisolone dose by 50%
to 30 mg/d

↓

4-6 months

5-10 mg/d of Prednisolone
or discontinuation of it

Cyclophosphamide

IV Cyclophosphamide

15 mg/kg every 2 weeks
for 3 doses

↓

15 mg/kg every 3 weeks
for 3-6 months

0.5 g/m² every 2 weeks
for 3-6 months

WBC>3500/µL and
absolute neutrophil count>1000/µL

↓

the dose increases to
0.75 g/m²

Oral Cyclophosphamide

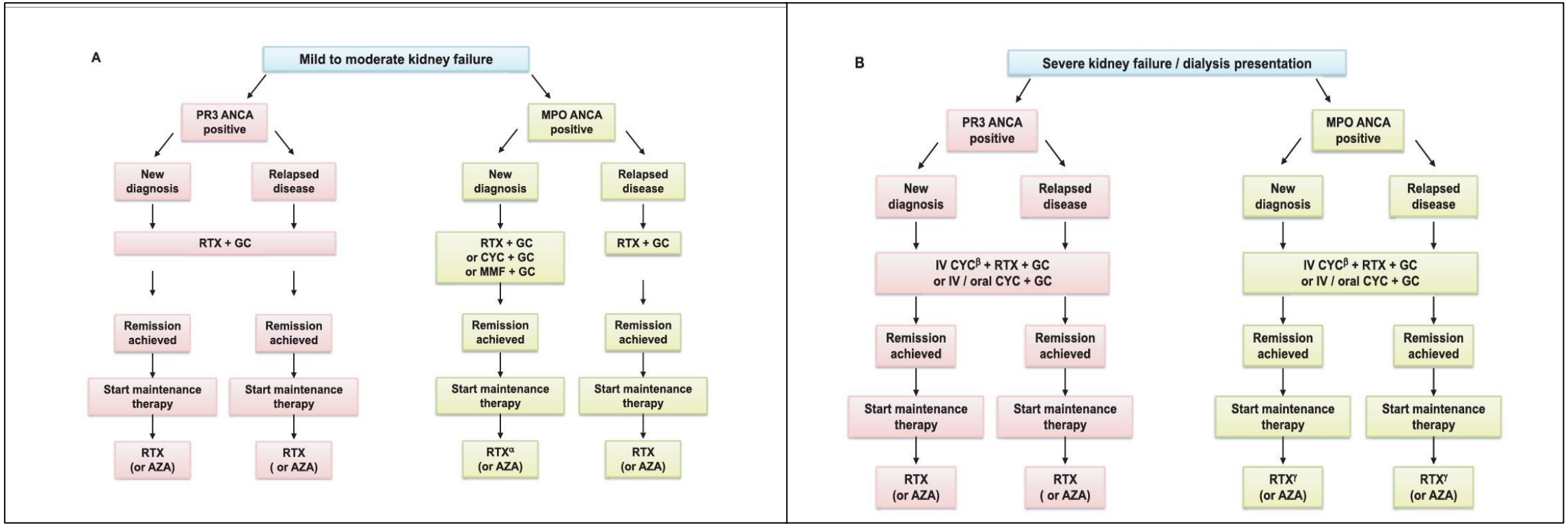
1.5-2 mg/kg
for 3-6 months

Adjustment of dose to keep
WBC>3500/µL and
absolute neutrophil count>1000/µL

Rituximab

375 mg/m²/ week for four
doses

1 g for two doses with an
interval of 14 days



The administration of glucocorticoids with both rituximab and cyclophosphamide has been suggested based on many observational studies. However, the benefit of this approach is not proven, and the risk of neutropenia, hypo-gammaglobulinemia and severe infectious complications is high with this combination therapy.

Geetha D and Jefferson J.A., AJKD 2020 ; 75: 124-37

Specific side effects of immunosuppressive medications for induction therapy in AAV

Immunosuppressive medication	Specific side effects	Considerations
Glucocorticoids	Infection, bone disease, hyperlipidemia, obesity, hypertension, GI bleeding, psychosis, cataract, adrenal disease, avascular necrosis of femoral head, cardiovascular disease.	Recent trials are focusing on steroid sparing approaches (PEXIVAS and Avacopan trials)
Cyclophosphamide	Bone marrow suppression Infection Hemorrhagic cystitis Malignancy (usually skin, bladder and myeloid malignancies, especially with cumulative dose of >36 g) Infertility Azoospermia (increasing with cumulative dose of >10 g)	1. CBC should be checked every 2 weeks during treatment with oral CYC and 10-14 days after each pulse with IV CYC. 2. The dose should be adjusted to maintain leukocyte count above 3500/µL 3. Patients on IV CYC should receive MESNA to protect bladder from acrolein toxicity. Although the efficacy of MESNA is not proven. 4. Semen cryopreservation for men ovarian suppression with gonadotropin-releasing hormone analogs in women is recommended.
Rituximab	Severe infection Hepatitis B and C virus reactivation Hypogammaglobinemia (50% of patients, rare in other diseases)	1. Immunoglobulin levels should be checked at baseline and and before each infusion. Some experts recommend to monitor immunoglobulins only in patients with frequent infection. 2. Rituximab should be avoided in those who are positive for HBS Ag or anti-HBc, without concurrent HBV therapy.

Back to the patient

A 52-year-old man with nasal discharge and sinusitis for 6 months was admitted to the hospital with massive hemoptysis. There was a history of progressive weight loss and weakness over 3 months. Serum creatinine was 6 mg/dl, and the PR3 ANCA was positive. The results of kidney biopsy revealed a diagnosis of pauci-immune crescentic GN.

He was treated with plasma exchange, glucocorticoid and IV cyclophosphamide. Six months after the induction therapy, the systemic symptoms and signs resolved and the urine sediment was inactive. But there was still 2+ proteinuria and a serum Cr of 2.5 mg/dl. The ANCA titer is still positive but with a lower titer compared to the admission value.

Question 2: Should we considered him a case of resistant to the chosen induction regimen?

Remission in patients with vasculitis and kidney involvement

Complete remission : The absence of active disease

Persistent proteinuria or even persistent renal insufficiency may be a result of irreversible injury rather than active disease.

Partial remission : The persistence of dysmorphic hematuria despite improvement in or stabilization of the serum creatinine and disappearance of extra-renal signs of active disease

Isomorphic hematuria in these patients may be a sign of cyclophosphamide-induced bladder toxicity.

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Question 2: Should we considered him a case of resistant to the chosen induction regimen?

- Patients in whom remission is not attain within 6 months should be considered to have resistant to the chosen induction regimen and need alternative regimens. But the presented patients is not a case of resistant to the induction therapy.
- The ANCA titer do not consistently reflect disease activity.
- Future trials should be performed before a treatment based on ANCA level can be recommended.

Maintenance therapy in the management of AAV

- **Relapse is common in AAV, occurring in 30 to 50% of patients by 5 years, often in the 12 to 18 months after discontinuation of immunosuppression.**

- **Maintenance immunosuppression is recommended following successful induction therapy to prevent relapse.**

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Question 3: What are the risk factors for prediction of relapse in this patients?

Factors increasing the risk of relapse

Demographics
- Younger patients

ANCA
- PR3-ANCA disease
- Persistence of ANCA after induction therapy
- Increase in ANCA titers (more predictive of renal relapse)

Clinical phenotype
- GPA
- Lung, upper respiratory tract, or cardiac involvement
- Preserved kidney function
- Prior relapses

Therapy related
- Discontinuation of immunosuppression (short duration of treatment)
- Lower cumulative dose of cyclophosphamide
- Discontinuation of prednisone
- Use of MMF for maintenance therapy
- B-cell reconstitution post rituximab

Other factors
- Chronic nasal carriage of *Staphylococcus aureus*
- HLA-DP1*04 alleles (in PR3-ANCA disease)

- **Recent literature has suggested that in patients renal involvement and/or alveolar hemorrhage, an ANCA rise is significantly associated with relapse.**

- **In patients without renal involvement ANCA can not be an accurate predictor of disease relapse.**

Geetha D and Jefferson J.A., AJKD 2020 ; 75: 124-37

Current guidelines for maintenance therapy in patents with ANCA-associated vasculitis are based on the following studies

Trial	Compared	The doses in remission phases	Results	Adverse effects
CYCAZAREM [1] 155 patients	CYC vs CYC/AZA	CYC 1.5 mg/kg/d vs AZT 2 mg/kg/d	Equal relapse rate	Similar Serious malignancies with CYC in long term
WEGNET [2] 126 patients	CYC/RTX vs CYC/MTX	AZT 2 mg/kg/d vs MTX 0.3 mg/kg/week initially, progressively rise to 25 mg/week	Equal relapse rate	Similar
IMPROVE [3] 156 patients	CYC/AZA vs CYC/MMT	AZT 2 mg/d for one year, 1.5 and 1 mg/d after 12 and 6 months MMT 2000 mg for 12 months and 1500 and 1000 mg/d after 12 and 18 months	Lower relapse with AZA at 39 months 38 vs 55(%)	Similar
MAINRITSAN [4] 115 patiets	CYC/RTX vs CYC/AZA	AZT 2 , 1.5, and 1 mg/kg/d for 12,6, and 4 months, respectively vs RTX two 500 mg separated by 2 weeks, Then at 6, 12, and 18 months	Lower relapse with RTX at 28 months 5 vs 29 (%)	Similar

CYC: cyclophosphamide, **AZA:** azathioprine, **MTX:** methotrexate, **MMT:** mycophenolate

1. Jayne D. N Engl J Med 2003; 349:36
2. Pagnoux C., et al. N Engl J Med 2008; 359: 2790
3. Hiemstra T.F., et al. JAMA 2010; 304:2381
4. Guillevin L., et al. . N Engl J Med 2014; 371: 1771

Maintenance therapy in patients with ANCA-associated vasculitis

Azathioprine

Initial dose 50 mg

Increasing the dose over several weeks

1.5-2 mg/kg/d
Maximum dose : 200 mg

Methotrexate

15 mg/week

Increasing the dose every 2-5 weeks

+5 mg/week
Up to 25 mg/week

Rituximab

Fix dosing strategy

500-1000 mg every 4-6 months

On-demand dosing strategy

Changing the dose by considering the number of CD 19 positive cell ANCA titer

Mycophenolate

1.5–2 g/d

After 18 months

1 g/d

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Question 4: Based on the current data what immunosuppressive regimen can be recommended as maintenance therapy for this patient?

Treatment strategies for remission maintenance in AAV

	No renal impairment	Renal impairment	Relapsing disease
PR3 ANCA	AZT, MTX, or MMF	RTX or AZT	RTX > AZT
MPO ANCA	AZT, MTX, or MMF	RTX, AZT, or MMF	RTX > AZT

There is no consensus about the duration of maintenance therapy

- **In most patients: 12 to 24 months after the remission**
- **Patients with multiple risk factors for relapse: 24 to 36 months after the remission**
- **The history of one or more previous relapse: indefinite therapy**

The role of IV Ig in management of ANCA-associated vasculitis

- The interference in ANCA binding to neutrophils by IV-Ig may inhibit ANCA-induced neutrophil activation.
- It seems that the effect of IV-Ig is not sustained for more than 3 months.
- Currently, IV-Ig is being used when a short term amelioration of disease activity is needed without increasing the risk of opportunistic infections.

Trimethoprim-sulfamethoxazole (TMP-SMX) in management of ANCA-associated vasculitis

- In patients who receive prednisolone ≥20 mg/d + cyclophosphamide/rituximab, TMP/SMX is recommended to prevent pneumocystis jirovercii (PCJ) infection.

- Moreover, a role of TMP-SMX has been suggested as an effective monotherapy in induction therapy of patients with GPA confined to the upper airway.

- There are evidence that the administration of TMP/SMX at higher doses than for PCJ prophylaxis during the maintenance therapy of ANCA-associated vasculitis is associated with lower rate of relapse.

Prognoses for GPA and APA

- Without treatment, the mortality rate is 90% within 2 years.
- Even with treatment the mortality rate is more than general population.
- The major cause of death are the complications of immunosuppressive therapy, complications of underlying disease, and the cardiovascular disease.
- The mortality rate is higher in older patients and patients with diffuse pulmonary hemorrhage requiring ventilator support or advanced kidney disease.
- The malignancy rate in GPA and MPA is higher than general population. (10-25%)
- The rate of serious infection requiring hospital admission is 25 to 30 percent, with respiratory infection being the most common.

Management of hemodialysis patients with ANCA-associated vasculitis

- About 20-25% of patients reach ESKD.
- In patients with dysmorphic RBC, immunosuppressive therapy is continued because the control of active disease may result in recovery of renal function.
- Withdrawal of immuno-suppressive therapy may be considered after 6 months in those with no extra-renal manifestation.
- The rate of relapse in hemodialysis patients is very low (0.08 episode per person per year)

Treatment of patients with double positive ANCA and Anti GBM

- Patients who are double positive for ANCA and anti GBM should be managed with plasmapheresis plus immunosuppressive therapy.

- As ANCA positive vasculitis has a tendency to relapse, unlike patients with single positive anti GBM, patients with double positive ANCA and anti GBM require maintenance therapy

Five factor score (FFS) in assessing severity of EGPA

- Age> 65
- Cardiac insufficiency
- Gastrointestinal involvement
- Renal insufficiency, Cr> 1.5 mg/dL
- Absence of ear, nose and throat manifestations

None of above factors:	the score is 0
The presence of one factor:	the score is 1
The presence of 2 or more factor:	the score is 2

- Glucocorticoids are the mainstay of treatment (Grade 1A); however, in patients with FFS of 2 or more, the addition of cyclophosphamide is recommended (Grade 1B).

- For patients with a FFS of 1 (especially with cardiac or CNS involvement) the addition of cyclophosphamide is also suggested. (Grade 2c)

EGPA specific therapies

- The prevalence of EGPA is significantly lower than that of MPA or GPA. Moreover, EGPA is often excluded from many of the large controlled trials in the management of ANCA-associated vasculitis, leading to a lack of strong evidence for its management.

- After induction of remission with glucocorticoid or glucocorticoid + cyclophosphamide, transition to Azathioprine for maintenance therapy is recommended. Methotrexate and Leflunomide are alternatives for maintenance therapy.

- As IL5 has a central role in pathogenesis of EGPA by stimulating eosinophilic activity, in December 2017, the FDA approved mepolizumab (an anti-IL5) , for the treatment of adult with EGPA.

- The effect of maintenance therapy with mepolizumab in the treatment of vasculitis manifestations is unclear. However it is effective in decreasing the doses of glucocorticoids and alleviating asthma and allergic symptoms.

Summary

- Prompt diagnosis and rapid initiation of effective treatment are the most important factors in treatment of AAV.
- The main therapy for remission induction of AAV is still GC and CYC. RTX is an effective alternative to CYC in treatment of AAV, especially in PR3 ANCA vasculitis.
- Based on PEXIVAS trial low dose GC therapy is non- inferior to high dose GC in induction therapy of AAV.
- Avacopam, a C5A inhibitor, is a promising new therapy that may replace high dose GC.
- For maintenance therapy, AZA or MTX are recommended. But RTX has also proven to have a role as an alternative maintenance therapy.
- The optimal length of maintenance therapy is still controversial.
- In the future, other tests that are highly correlated with relapse activity should be combined with ANCA for therapeutic guidance.