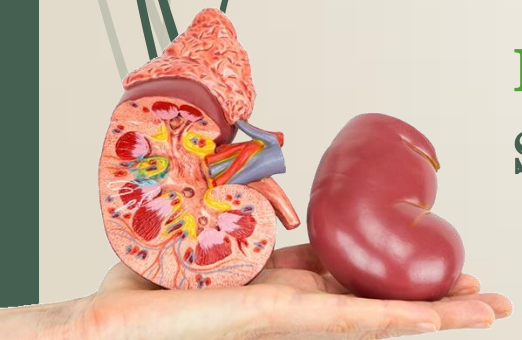
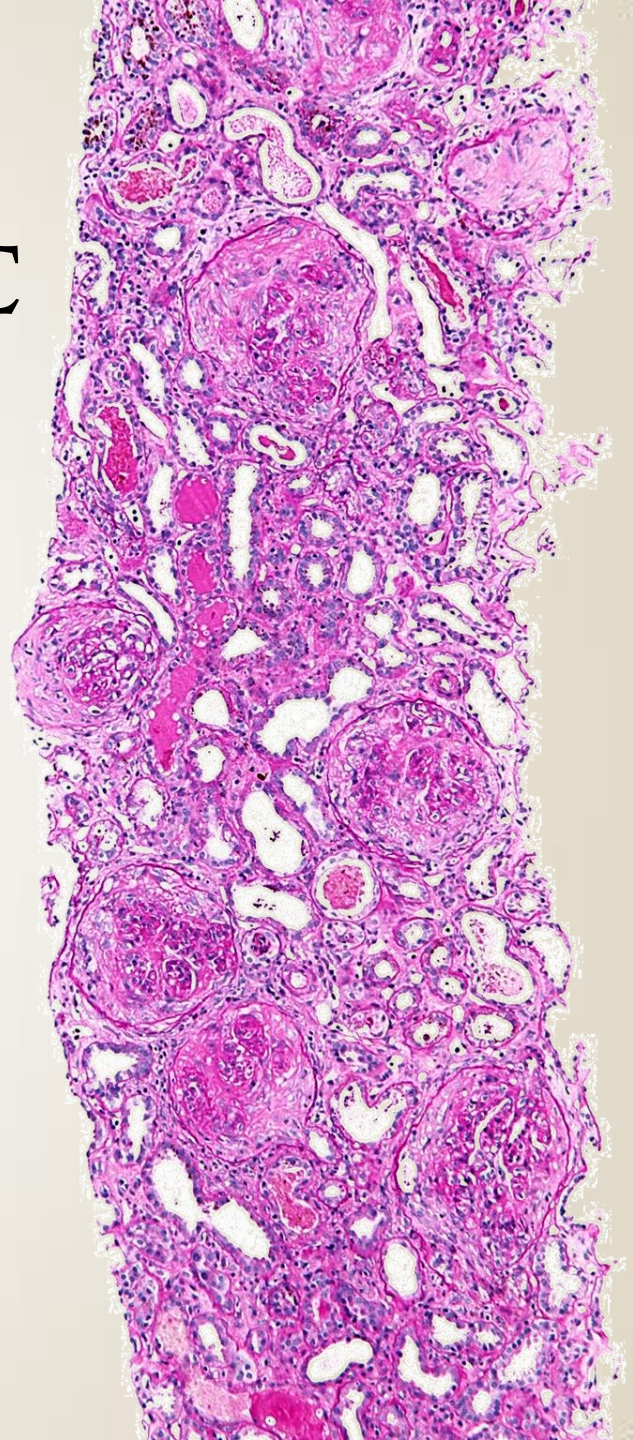

بسم الله الرحمن الرحيم

# PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS

## Treatment and Prognosis





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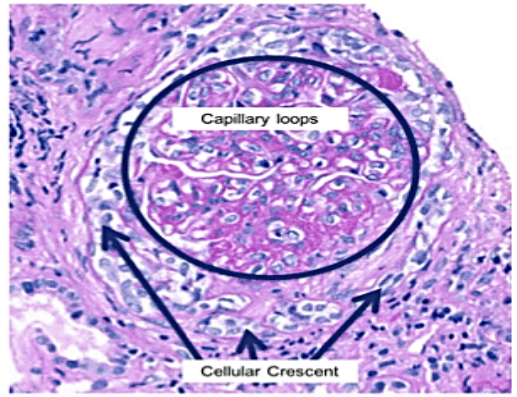
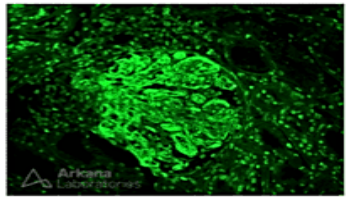
## Rapidly Progressive Glomerulonephritis (RPGN)

- Loss of kidney function over a **short period of time**
- Urinalysis with evidence of glomerular disease **(hematuria, proteinuria)**
- Crescent formation **(extra-capillary proliferation in Bowman's space)**



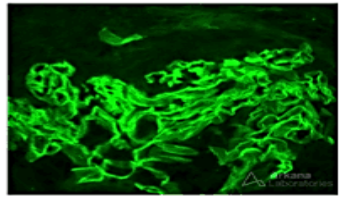

### Immune-Complex Mediated

- **Presence of immune deposits in glomeruli**
- Ex: IgA nephropathy, lupus nephritis, cryoglobulinemia, post-infectious GN



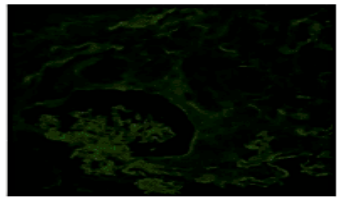
### Anti-Glomerular Basement Membrane (GBM)

- Typically **circulating autoAb against type IV collagen (α3 chain)**
- Linear, ribbon-like GBM staining on IF
- No EM deposits



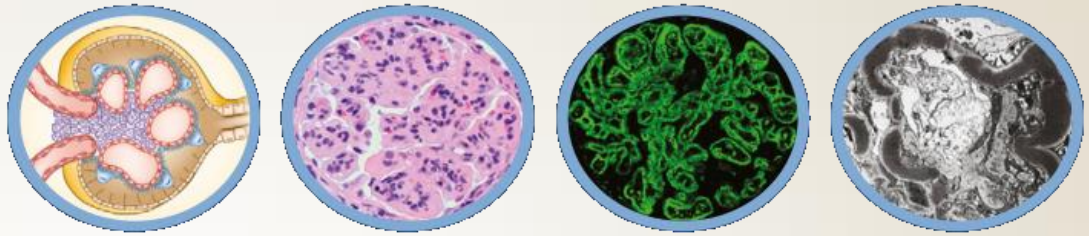
### Pauci-Immune

- Minimal immune deposits, negative IF
- **Majority anti-neutrophil cytoplasmic antibody (ANCA) +**
- **c-ANCA**: anti-proteinase 3 (CPR) → cytoplasmic neutrophilic staining
- **p-ANCA**: anti-myeloperioxidase (MPO) → perinuclear cytoplasmic staining



NephSim
www.nephsim.com

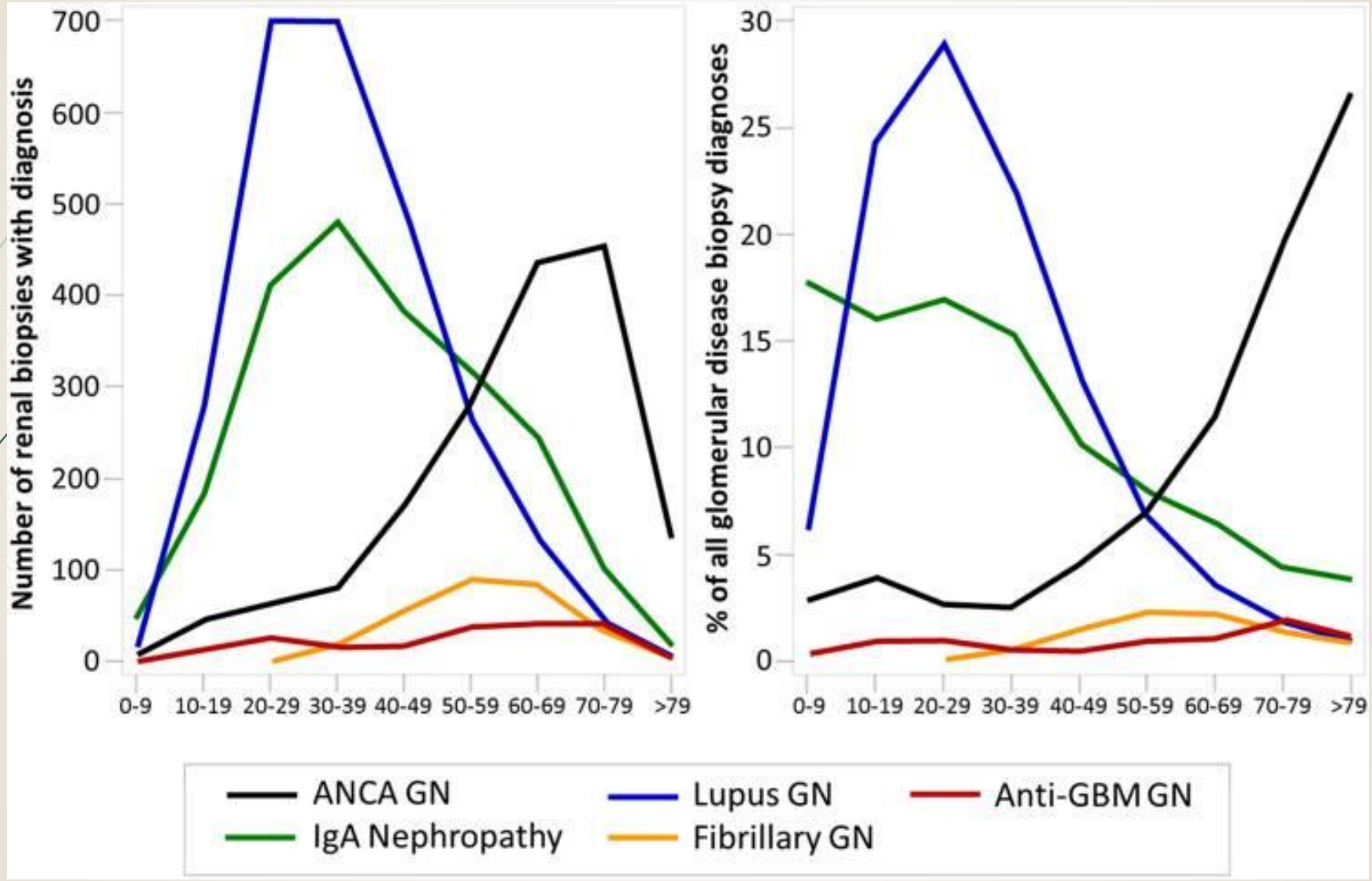
# Definition



- Pauci-immune glomerulonephritis is one of three types of isolated **renal vasculitides** (the other two being immune complex–mediated glomerulonephritis and Goodpasture syndrome).
- Pauci-immune glomerulonephritis lacks any immunoreaction product except for minimal accumulation of **fibrin**.
- Anti-neutrophil cytoplasmic antibody (**ANCA**)-associated vasculitis is the most common cause of rapidly progressive glomerulonephritis worldwide, and the renal biopsy is the gold standard for establishing the diagnosis.

**J Am Soc Nephrol 21: 1628 –1636, 2010.**

# Prevalence

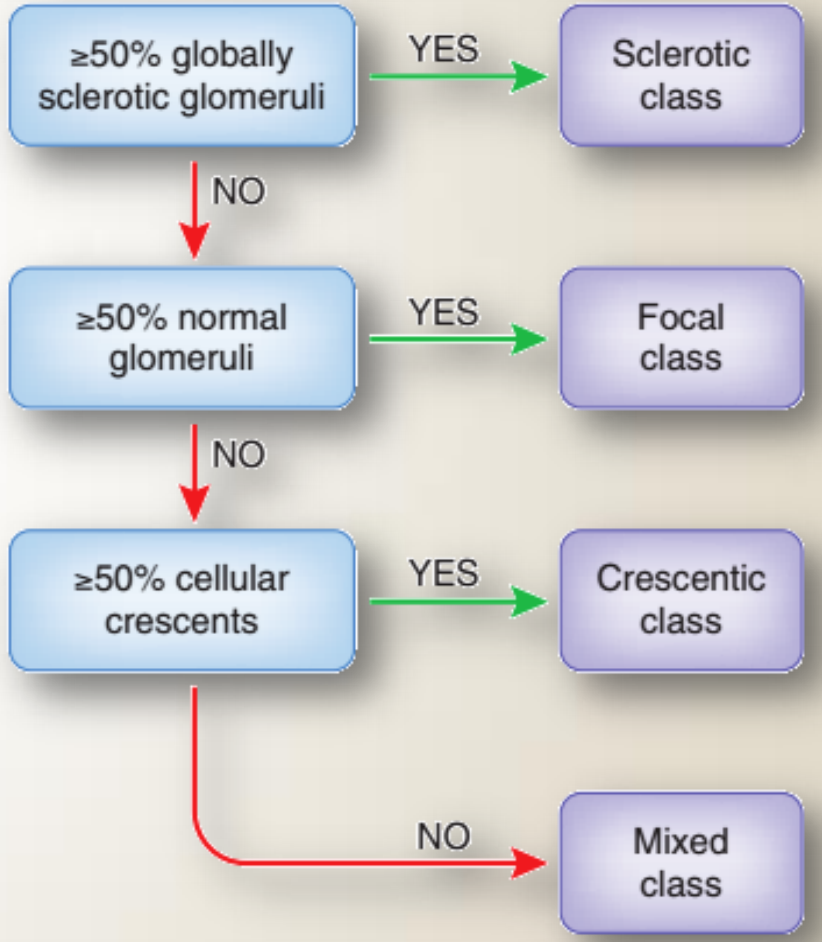



Clin J Am Soc Nephrol. 2017; 12(10): 1680–1691

# Histopathologic classification

Classification proposes four general categories of lesions:

**Focal**, **crescentic**, **mixed**, and **sclerotic**




J Am Soc Nephrol 21: 1628 –1636, 2010.

# Characteristics of the disease

- (ANCA)-associated vasculitis, particularly **Wegener's granulomatosis** and **microscopic polyangiitis**, often affect the kidneys, and **renal involvement** is an important factor with respect to patient **morbidity** and **mortality**.
- ANCA-associated glomerulonephritis is characterized on immunofluorescence microscopy by little or no glomerular staining for IgG or complement, the so-called pauci-immune staining pattern. By electron microscopy, **subendothelial edema**, **microthrombosis**, and **degranulation of neutrophils** are present.
- In the kidney, partial remission refers to the persistence of dysmorphic (ie, glomerular) **hematuria**. Persistent **proteinuria** may reflect irreversible glomerular injury and, as an isolated finding, is not indicative of active disease.

**J Am Soc Nephrol 21: 1628 –1636, 2010.**

# Conventional treatment

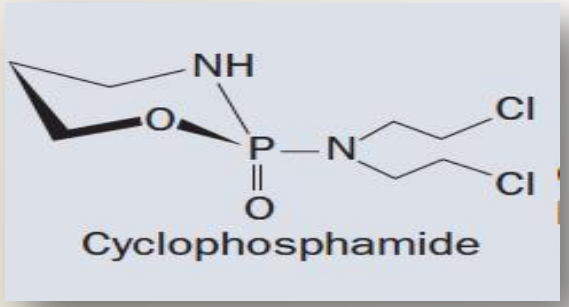
For decades, conventional treatment of ANCA disease with major organ involvement has been with high-dose cyclophosphamide and glucocorticoids, which has induced remission in approximately 75% of patients at 3 months and up to 90% at 6 months, although relapses and adverse side effects were frequent.

More recently, new treatment regimens have been developed to limit the dose of cyclophosphamide and glucocorticoid exposure during both the induction and maintenance phases.

Blood Purif 2018;45:213–217

# Treatment

According to the current guidelines the induction treatment of systemic generalized ANCA-associated vasculitis (AAV) should consist of either **cyclophosphamide (CTX)** or **rituximab (RTX)** with **corticosteroids (CS)**, with the addition of **plasma exchange (PLEX)** recommended in patients with severe renal involvement (S-creatinine ≥ 500 µmol/L) and/or alveolar hemorrhage.

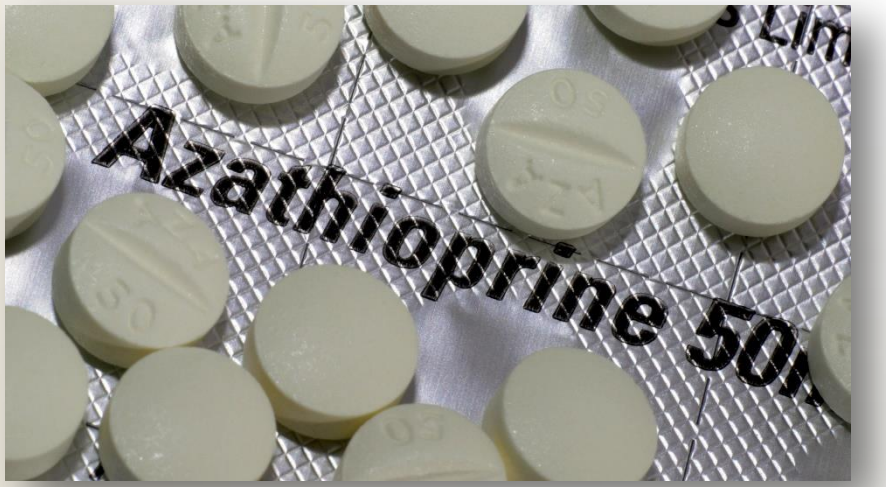




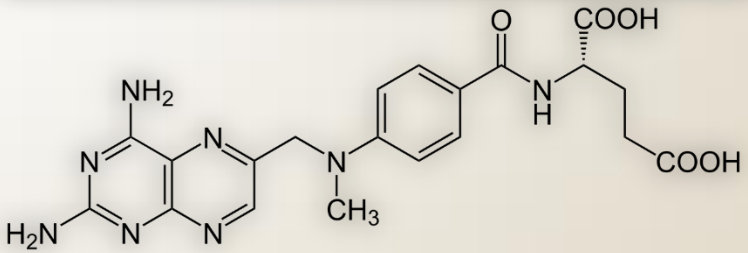
**Blood Purif 2018;45:213–217**

# Maintenance treatment

In the maintenance treatment, **azathioprine** or **methotrexate** (with low-dose corticosteroids) are most commonly used, but **RTX** has been also increasingly used in this setting and successfully tested as a maintenance agent in a clinical trial.








**Blood Purif 2018;45:213–217**

# AAV management IN THE ELDERLY

- Elderly patients with AAV who received **immunosuppressive treatment** had better prognosis (lower mortality and/or lower number of ESRD) than those left untreated or not treated in the standard way.
- The older patients were more likely to develop **infection**, particularly if **leukopenia** was present.

**Clin J Am Soc Nephrol 2015;10:1128–1135.**

# Resistance to the treatment

- **Resistance**, defined as a progressive decline in kidney function (ie, increase in serum creatinine), with persistent active urine sediment, or persistence, or new appearance of any extra-renal manifestations.
- There are also patients who initially responded to therapy that let them escape life-threatening organ damage, never achieved complete obliteration of the pathogenic process, maintaining a low grade of persistent **'grumbling disease'**.

**Kidney Dis 2015;1:224–234**

# Resistance to the treatment

- Predictors in a large cohort of patients with AAV, recruited by kidney disease, showed that **23% of the 334 treated patients** became treatment-resistant. The majority **developed ESRD** within a median of 2 months after starting therapy.

- **Female sex**, **black ethnicity** and **severity of renal involvement** were identified as predictors of treatment resistance.

**Clin J Am Soc Nephrol 2014;9:905–913; Arthritis Rheum 2000;43:1021–1032.**

# Induction Therapy

- The gold standard of treatment in AAV is the combination of corticosteroids with the cytotoxic agent cyclophosphamide given as  IV or P.O and pulses of methylprednisolone. Reducing the dosage in a gradual over the next 3–5 months.
- Cyclophosphamide is given either monthly, intravenously starting at a dose of 0.5 g/m 2 of body surface area, subsequently increased up to 1 g/m 2 of body surface area, or orally at an initial dose of 2 mg/kg of body weight/day.

# Rituximab pharmacology

- **Targeted B cell therapy** to eliminate pathogenic ANCA is conceptually attractive because this could selectively **reduce antibody production** while preserving other adaptive and innate immune cells.


- Rituximab, which is an mAb that targets **CD20 on B cells**, is an alternative to cyclophosphamide.

# Rituximab

- Owing to its success in randomized trials, RTX now represents (at least) a comparable alternative for both **induction and maintenance treatment of AAV**, especially in **relapsing vasculitis** even though it has been increasingly used also as a **first-line treatment option**.

- These are manifested as vasculitic signs or symptoms in any organ system, although **relapses** tend to affect the same organ systems as on initial presentation, with **new organ involvement** reported only in **23% of patients.**


**N Engl J Med 2014;371:1771–1780; N Engl J Med 2010;363:211–220; J Am Soc Nephrol 1996;7:33–39**

# Rituximab

- Timlin et al. used RTX as induction treatment in 31 elderly patients with AAV (mean age 71 ± 6 years, 22 patients [71%] with renal involvement).

- **Remission was achieved in 97% of patients**, and the safety profile of RTX in elderly patients seemed good, BUT the incidence of **INFECTION** was relatively high.


Blood Purif 2018;45:213–217

# Rituximab

- Two trials showed that rituximab was noninferior for inducing remission compared with iv cyclophosphamide (RITUXIVAS trial) or oral cyclophosphamide (RAVE trial).
- Adverse events were not reduced in the patients treated with rituximab in either trial.
- percentage of peripheral blood CD5-positive regulatory B cells is a useful indicator of disease activity, remission, and future relapse after rituximab therapy, and thus may help measure the effectiveness of induction therapy and guide maintenance therapy for relapse.


**Blood Purif 2018;45:213–217**

# Rituximab

- Rituximab is another option for maintenance of remission.
- Rituximab was better than azathioprine for preventing relapse, including renal relapse.
- The optimum duration of maintenance therapy depends on multiple factors. Ending too soon increases the risk of relapse.


Blood Purif 2018;45:213–217

# cyclophosphamide

- The duration of therapy with cyclophosphamide is usually **6–12 months**, depending on the patient's initial response. Both **oral and intravenous** administrations of cyclophosphamide have been proven equally potent inductors of remission in AAV, but its cumulative dose is significantly lower in parenteral administration.

**The rituximab-based regimen was shown to be more efficacious than the cyclophosphamide- based regimen for inducing remission in patients with relapsing disease.**

**Kidney Dis 2015;1:224–234; Blood Purif 2018;45:213–217**

# Response to Immunosuppressive Therapy and Long-Term Outcomes

Immunosuppressive therapy in AAV aims at induction of **remission**, defined as:

- ✓ **stabilization or improvement of kidney function**
- ✓ **resolution of hematuria**
- ✓ **all other organ-specific vasculitic manifestations**

J Am Soc Nephrol 1996;7:33–39

# Treatment

- One study of 155 patients with GPA or MPA and crescentic glomerulonephritis, 87 percent required hemodialysis at the time of kidney biopsy.
- **Renal remission** — If there is no active renal inflammation, then hematuria and, if present, red cell casts should remit.
- **Remission** is defined in such patients as less than 5 red cells per high-power field. Persistent hematuria should raise concern for ongoing glomerulonephritis.
- The hematuria due to bladder injury should resolve within three to four weeks after the last cyclophosphamide dose.

# Plasmapheresis study

- Plasmapheresis has therapeutic effect in patients with ANCA disease (including ANCA plus anti-GBM disease)
- Renal impairment (serum creatinine .6 mg/dl or requiring dialysis),
- Alveolar hemorrhage.
- Plasmapheresis was associated with increased rate of renal recovery compared with methylprednisolone at both 3 and 12 months of follow-up.
- Severe adverse event rates and patient survival were similar in both groups.

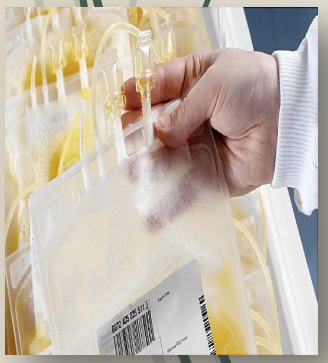
# Plasmapheresis

- In a meta-analysis on 387 patients, the addition of plasma exchange to standard care **decreased the pooled risk of end-stage renal disease or death**.
- For patients with **severe renal disease**, who have pulmonary hemorrhage, **seven sessions of plasma exchange over two weeks (60 mL/kg at each session)**.

# Plasmapheresis

- **Albumin** is the preferred replacement fluid in **patients without bleeding or a recent renal biopsy**.

- For patients with risk of **bleeding or a recent biopsy**, **1 to 2 liters of fresh frozen plasma be substituted for albumin** at the end of the procedure to reverse pheresis- induced depletion of coagulation factors.



# Plasmapheresis

- For patients with **active hemorrhage**, the replacement fluid should exclusively be **fresh frozen plasma**.
- Among patients who develop **severe infection** in the setting of plasma exchange, **a single infusion of intravenous immunoglobulin (100 to 400 mg/kg)** can be given .

# PEXIVAS: No benefit of plasma exchange in ANCA-associated vasculitis

The open-label trial with a two-by-two factorial design included 704 patients with severe ANCA-associated vasculitis (estimated glomerular filtration rate <50 mL/min per 1.73 $m^2$ or diffuse pulmonary hemorrhage) who received standard induction immunosuppressive therapy with either cyclophosphamide or rituximab.

**N Engl J Med 2020; 382: 622–631**

# Maintenance Therapy

- **Relapse** may occur in **30–50% of patients** achieving remission after the completion of induction therapy.
- Predictors of relapse among responders in AAV have been shown to be **PR3-ANCA seropositivity** as well as **pulmonary** and **ear/nose/throat involvement**, each associated with an approximately **2.0-fold increase in risk** for relapse

**Kidney Dis 2015;1:224–234**

# Maintenance therapy

1) **Azathioprine** suitable for maintaining disease remission, however had adverse event rate.

1) **Methotrexate** combined with corticosteroids showed remission rates of 60–90%, but elevated rate of relapse.

   Yet, the clinical experience with methotrexate is limited to patients with predominantly extra-renal manifestations of vasculitis and preserved renal function (serum creatinine <2.5 mg/dl).

**JAMA 2010;304:2381–2388; Arthritis Rheum 1999;42:2666–2673; Arthritis Rheum 2000;43:1836–1840**

# Maintenance of Remission

- **Azathioprine** once complete remission is attained demonstrated no difference in outcome including relapse rate. Compared with azathioprine, maintenance therapy with **MMF** was associated with a significantly higher rate of relapse.

- **Methotrexate** may be useful in maintaining remission in patients with mild disease and no renal impairment.

JAMA 2010;304:2381–2388; Arthritis Rheum 1999;42:2666–2673; Arthritis Rheum 2000;43:1836–1840

# Predictors of Patient and Renal Survival

- Relative risk of death was almost nine times greater in patients who presented with **pulmonary hemorrhage** and four times greater in patients with cytoplasmic Versus perinuclear ANCA.
- The use of **cyclophosphamide** lowered the risk of death approximately six times when compared with Steroid therapy alone.
- **Age >50 years** at diagnosis, lung or kidney involvement were associated with an almost four-fold increased risk for death.
- strongest predictors of long-term renal survival were entry **serum creatinine value**, **black race** and **arterial sclerosis** on renal biopsy.

**Kidney Dis 2015;1:224–234**

# Relapse Treatment

- Patients with ANCA GN with severe kidney failure at the initiation of therapy have a low but not negligible response to treatment.
- Indicating that continued immunosuppressive therapy is unlikely to benefit patients who are dialysis dependent for 4 Months.

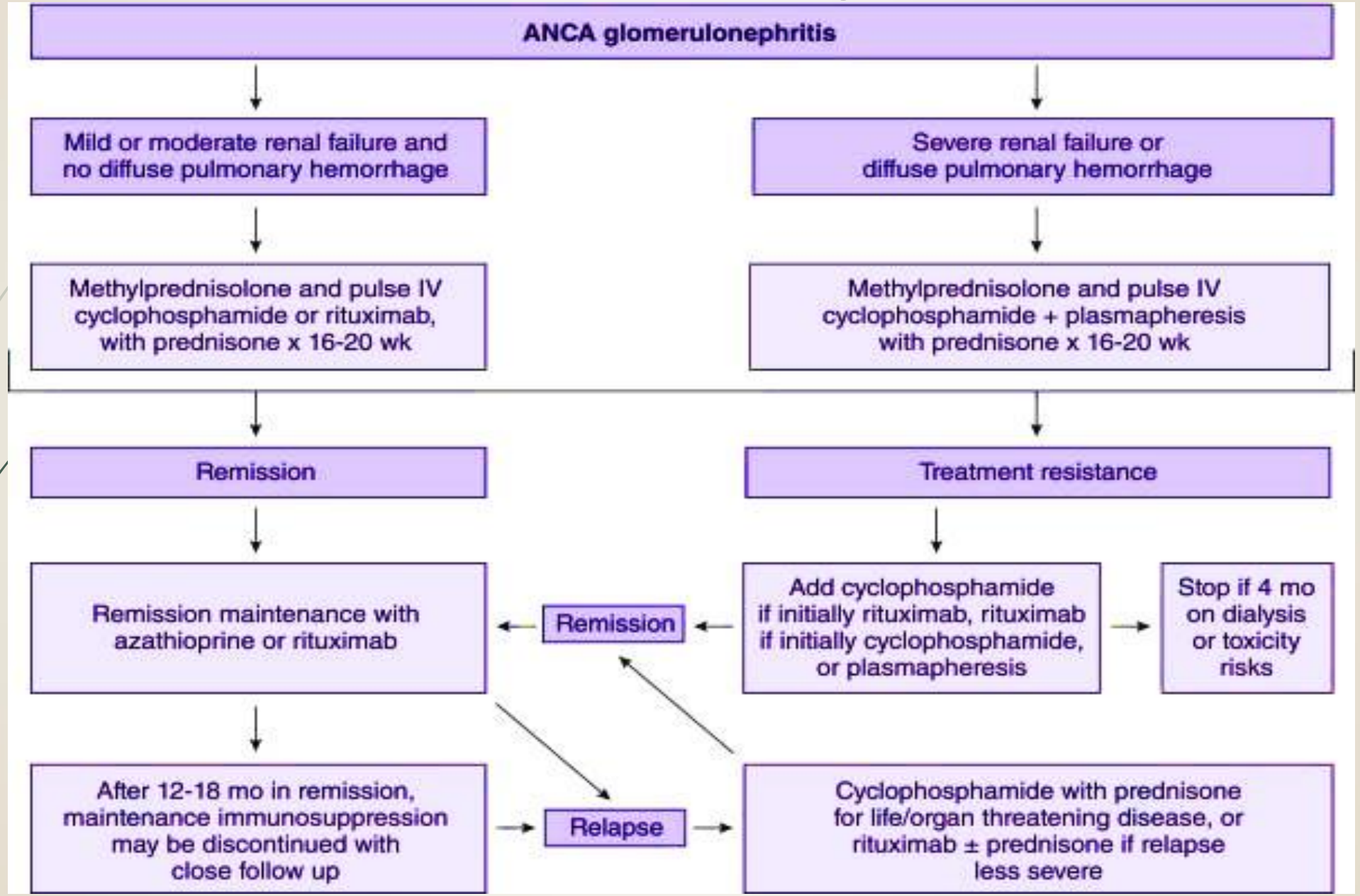
Kidney Dis 2015;1:224–234

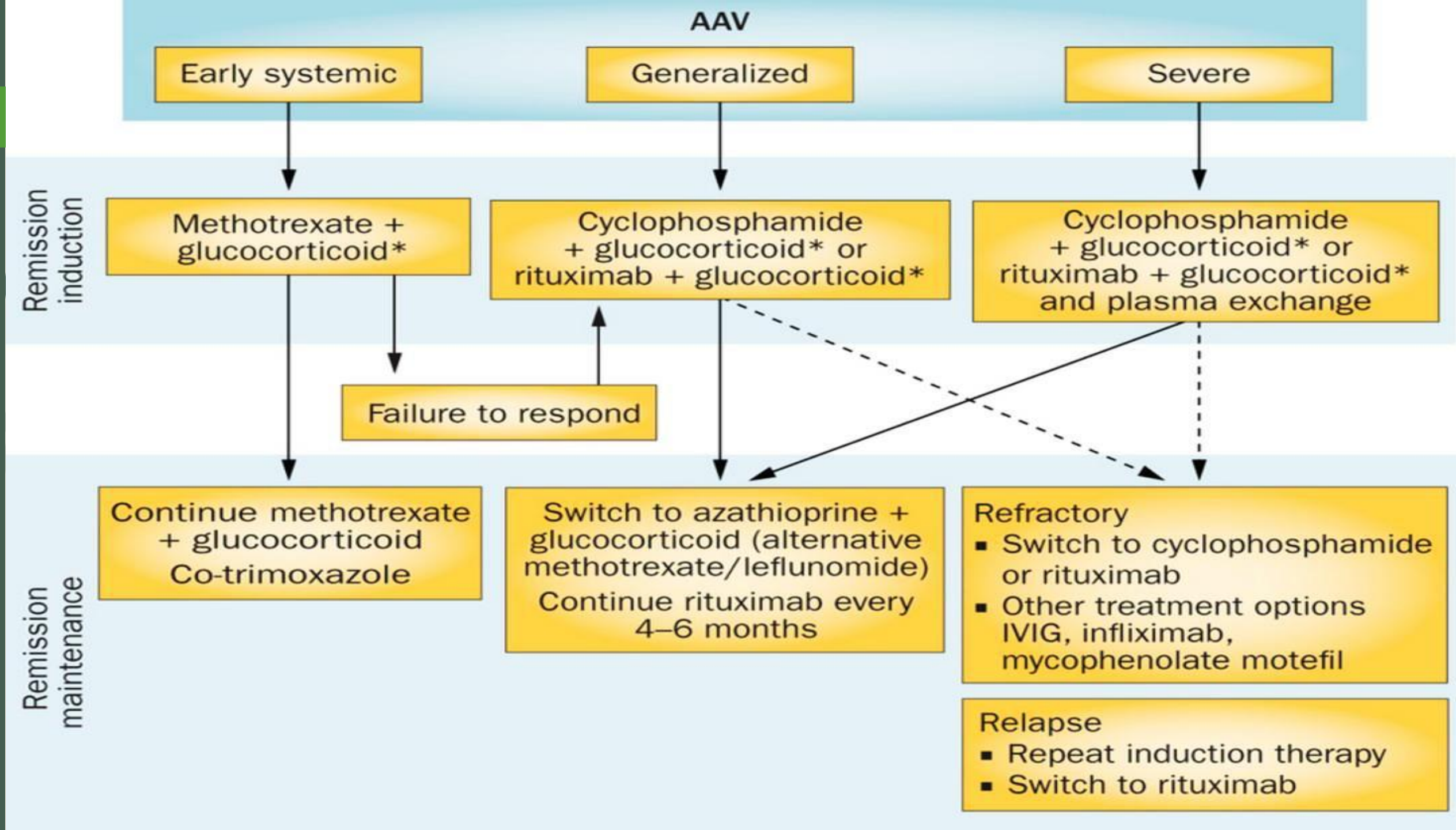
# Kidney TX  in AAV.

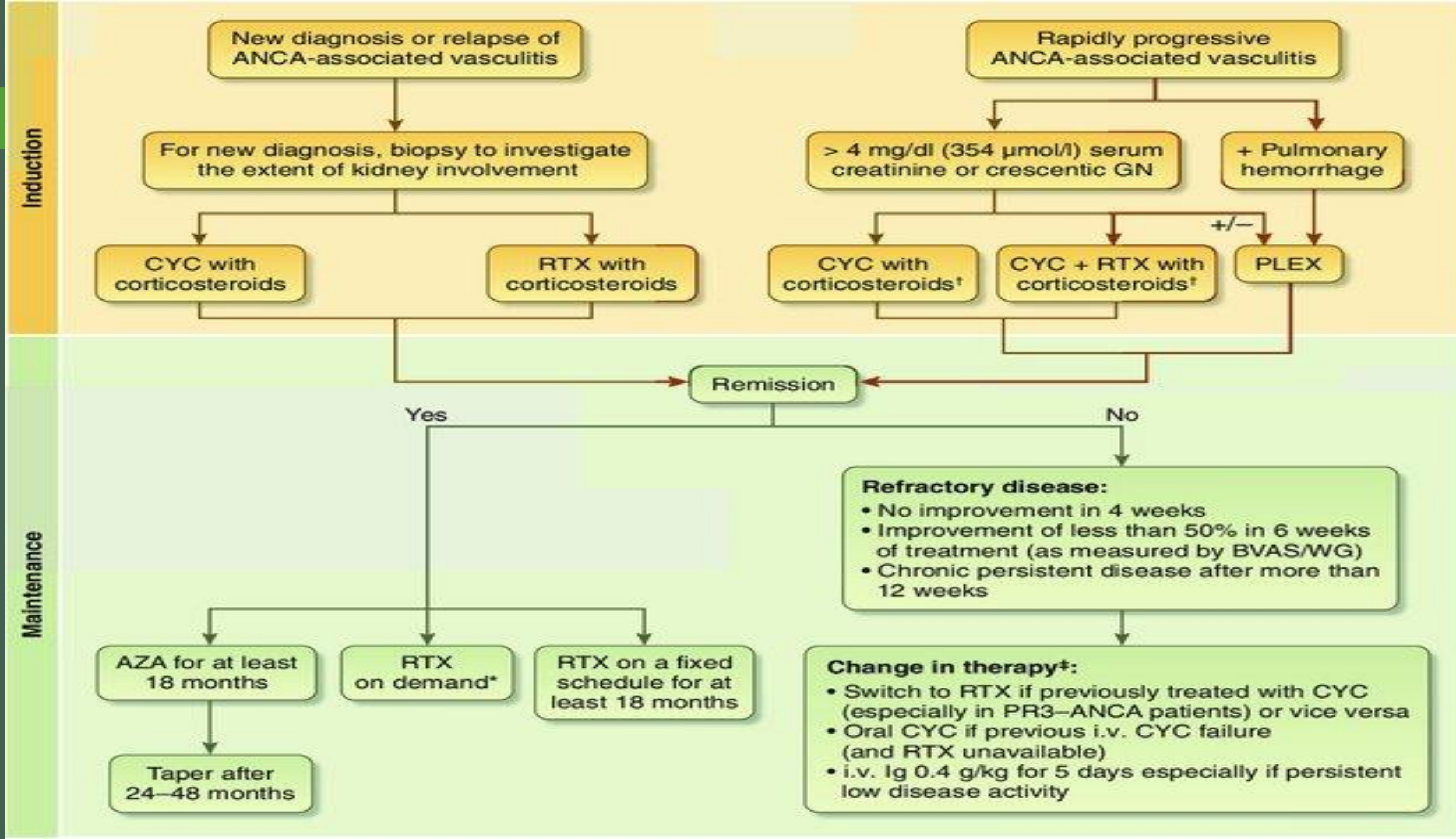
- For patients in **complete remission** and without extrarenal manifestations for at least 12 months, renal transplant should not be delayed.
- **ANCA positivity** is not considered a contraindication for transplantation. However, no prospective data are available to assess the likelihood of recurrent ANCA vasculitis after kidney transplantation.
- In addition, the impact of disease activity or ANCA positivity at the time of transplantation on patient outcome is unclear.

**https://www.uptodate.com/contents/treatment-and-prognosis-of-eosinophilic-granulomatosis-with-polyangiitis-churg-strauss**

# ANCA vasculitis treatments algorithm




AAV
Early systemic
Generalized
Severe
Remission induction
Methotrexate + glucocorticoid*
Cyclophosphamide + glucocorticoid* or rituximab + glucocorticoid*
Cyclophosphamide + glucocorticoid* or rituximab + glucocorticoid* and plasma exchange
Failure to respond
Remission maintenance
Continue methotrexate + glucocorticoid
Co-trimoxazole
Switch to azathioprine + glucocorticoid (alternative methotrexate/leflunomide)
Continue rituximab every 4–6 months
Refractory
Switch to cyclophosphamide or rituximab
Other treatment options IVIG, infliximab, mycophenolate motefil
Relapse
Repeat induction therapy
Switch to rituximab


Induction
New diagnosis or relapse of ANCA-associated vasculitis
For new diagnosis, biopsy to investigate the extent of kidney involvement
CYC with corticosteroids
RTX with corticosteroids
Rapidly progressive ANCA-associated vasculitis
> 4 mg/dl (354 µmol/l) serum creatinine or crescentic GN
+ Pulmonary hemorrhage
+/−
CYC with corticosteroids†
CYC + RTX with corticosteroids†
PLEX
Remission
Yes
No
Maintenance
AZA for at least 18 months
Taper after 24–48 months
RTX on demand*
RTX on a fixed schedule for at least 18 months
Refractory disease:
• No improvement in 4 weeks
• Improvement of less than 50% in 6 weeks of treatment (as measured by BVAS/WG)
• Chronic persistent disease after more than 12 weeks
Change in therapy‡:
• Switch to RTX if previously treated with CYC (especially in PR3–ANCA patients) or vice versa
• Oral CYC if previous i.v. CYC failure (and RTX unavailable)
• i.v. Ig 0.4 g/kg for 5 days especially if persistent low disease activity

# Thanks for your attention