Small Vessel Vasculitis
Update on Management

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CME Disclosure Statements

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Unlabeled use of commercial products

To date there are two FDA approved agents for the treatment of ANCA vasculitis

All other references to use of a commercial product for the treatment of ANCA vasculitis discussed in this presentation constitute an unlabeled use of the product

Speaker relationship to commercial products

Provide funding for clinical trials on which the speaker is an investigator

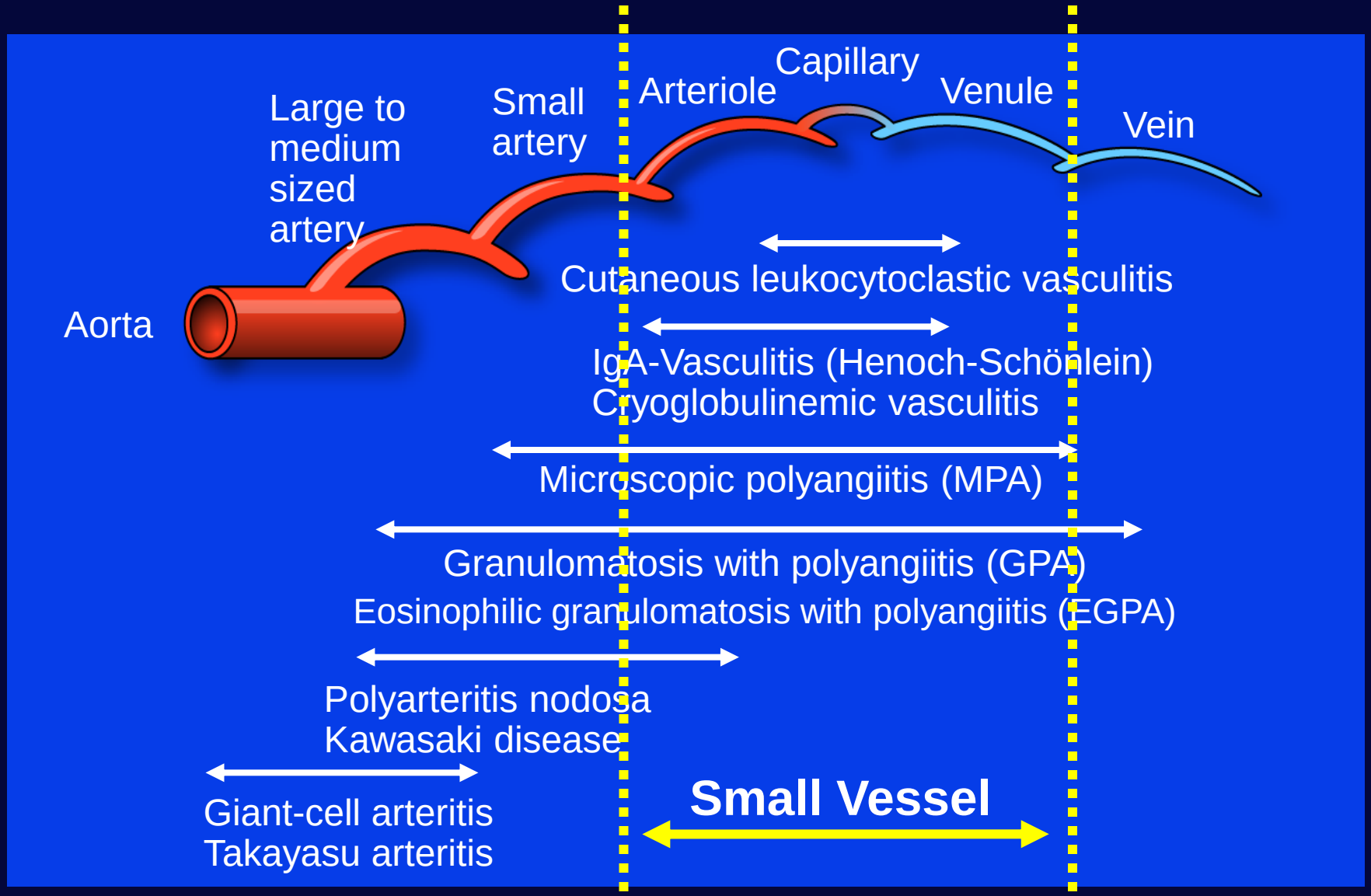
- Bristol-Myers Squibb
- GlaxoSmithKline
- AstraZeneca
- NS Pharma

Non-paid consultant: Bristol-Myers Squibb, AbbVie, AstraZeneca

Topics for Today's Discussion

- Brief clinical overview that influences treatment decisions
- Treatment options in 2025
  - Induction of remission
  - Remission maintenance
- Plasma exchange
- Avacopan
- ANCA vasculitis – what lies ahead

Nomenclature of Primary Vasculitis
Chapel Hill Consensus Conference



Jennette et al. Arthritis Rheum 2013; 65:1

Nomenclature of Primary Vasculitis
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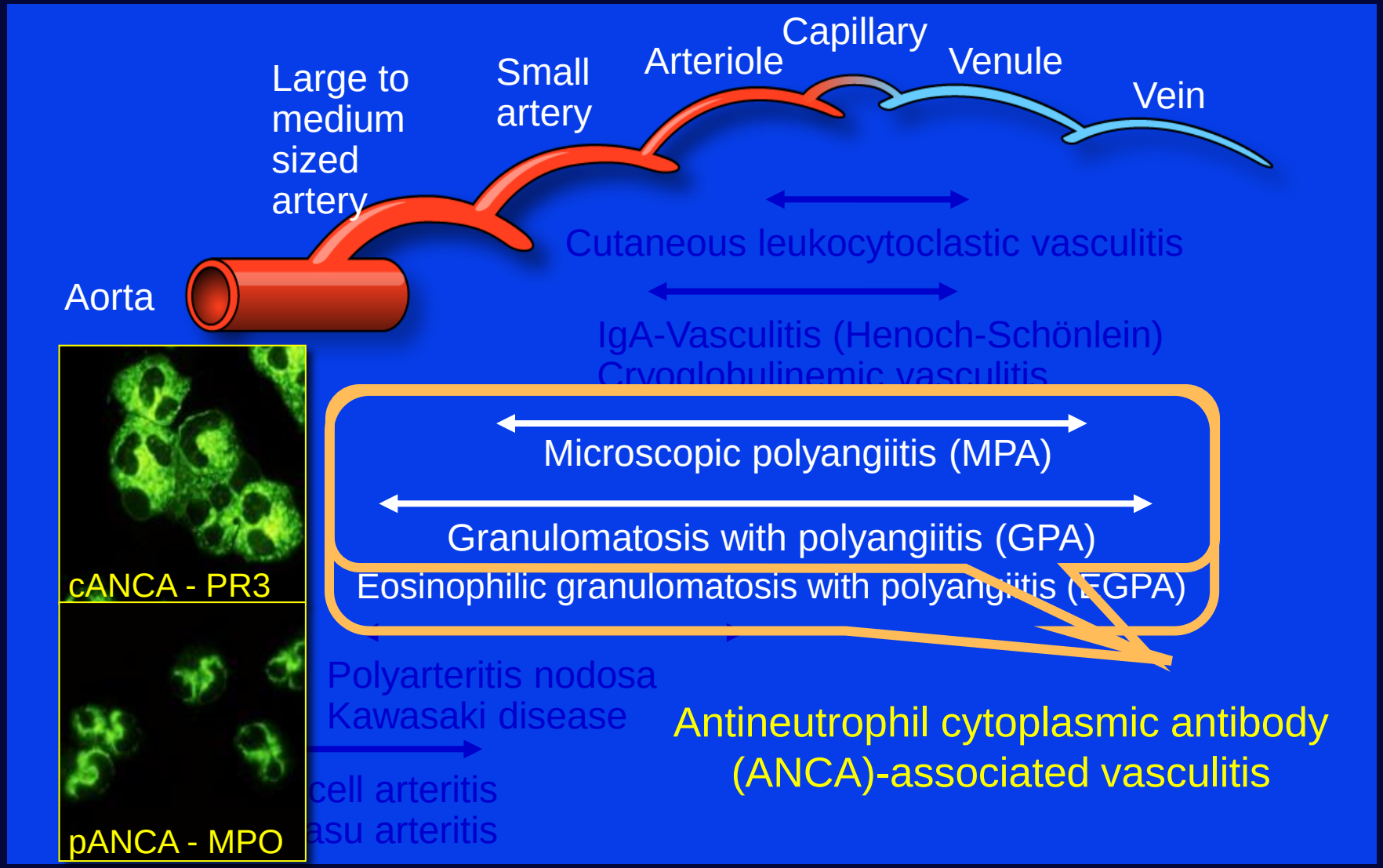
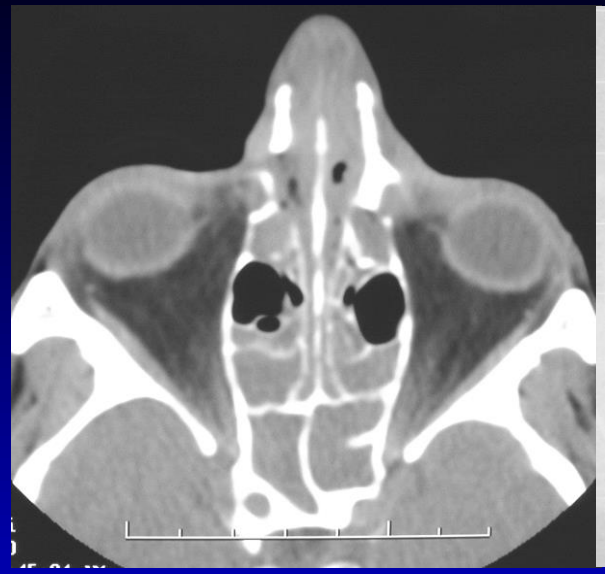
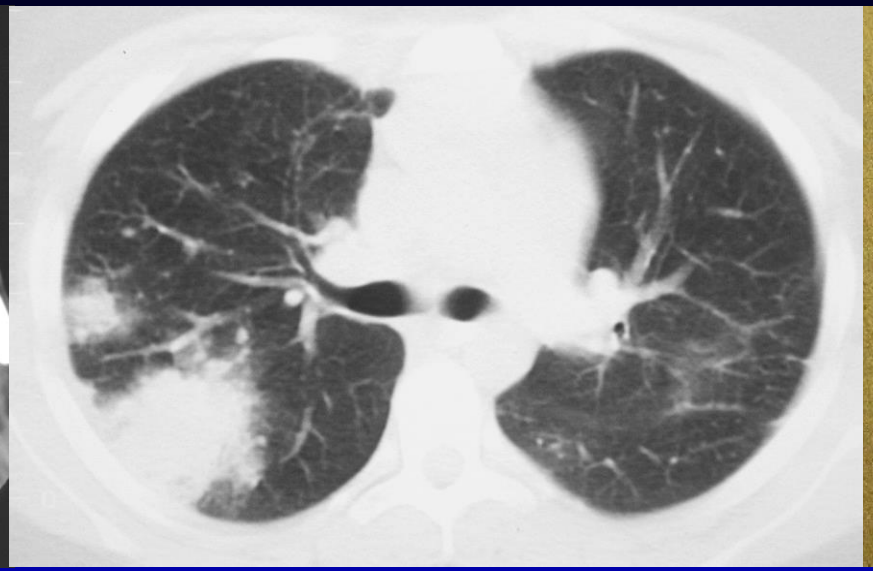


Jennette et al. Arthritis Rheum 2013; 65:1

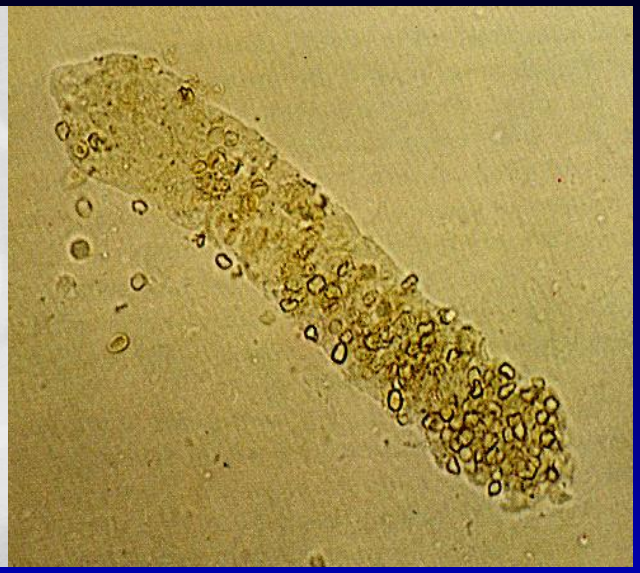
upper airways



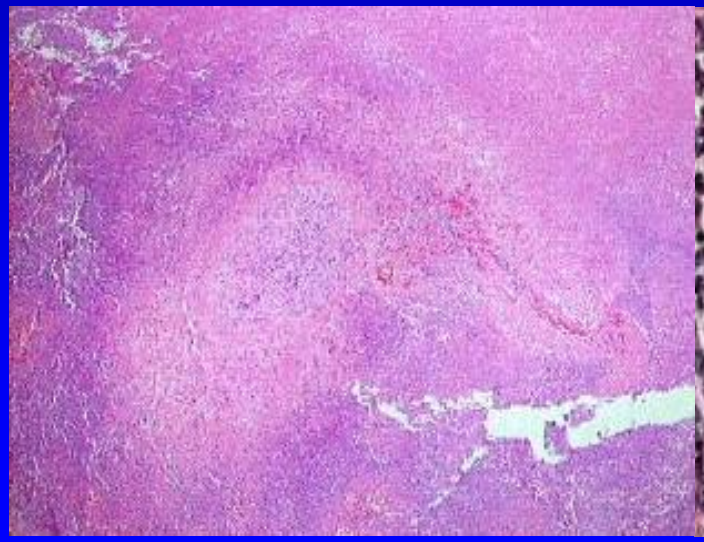
lungs



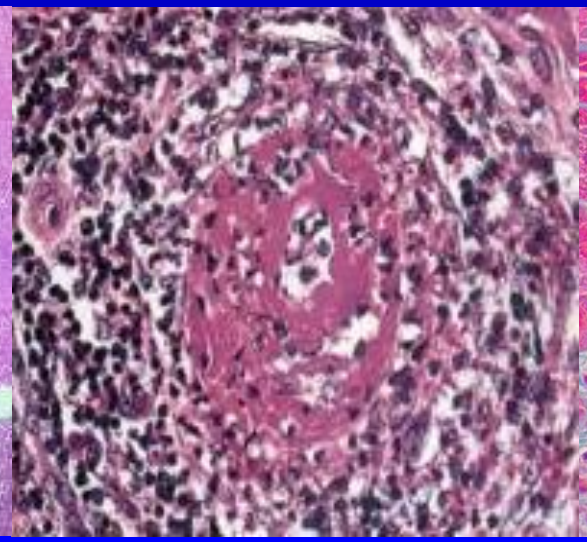
kidneys



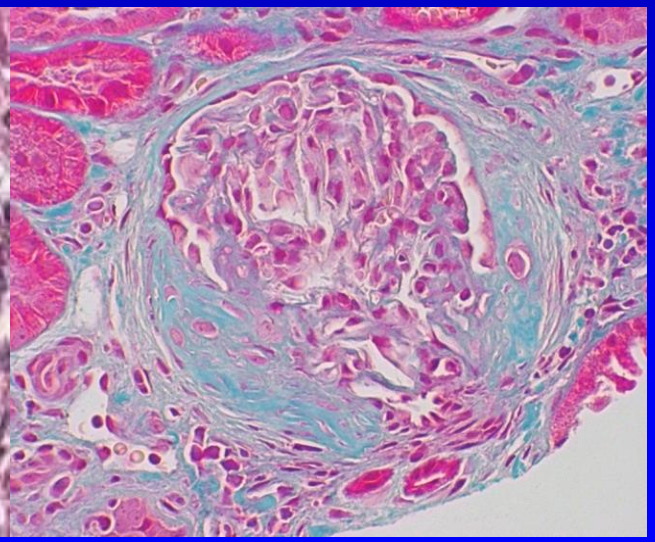
Granulomatosis with Polyangiitis



granulomatous inflammation

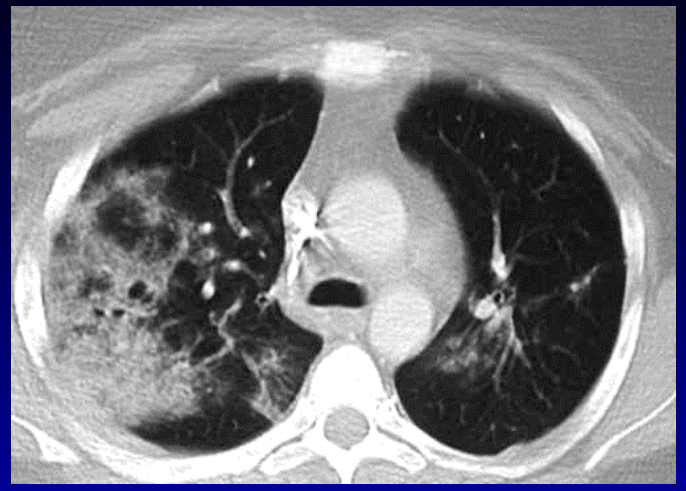


vasculitis

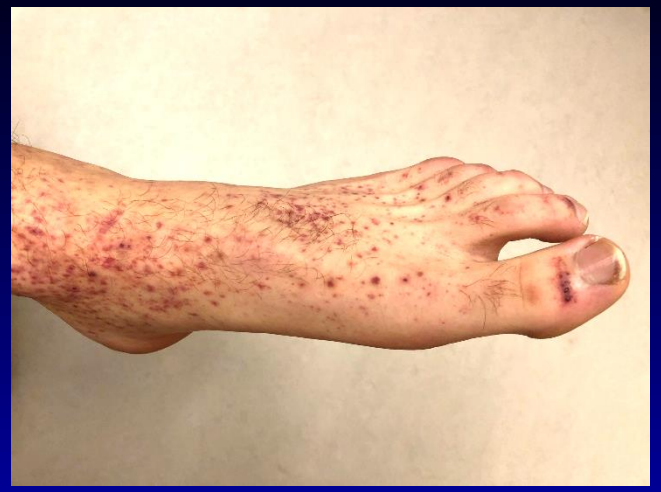


glomerulonephritis

lungs

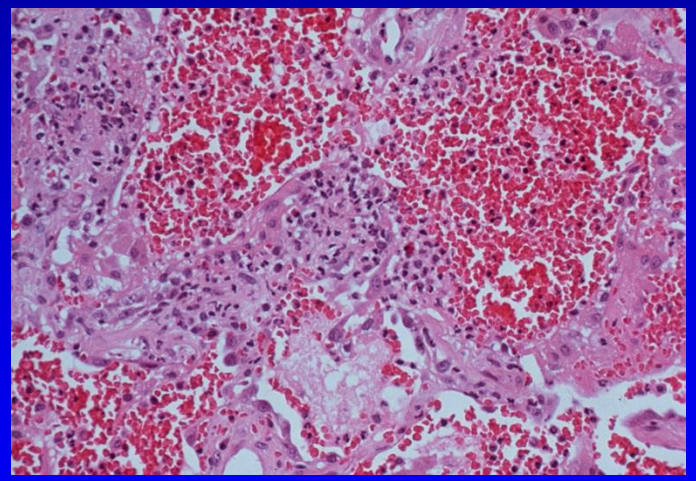


skin



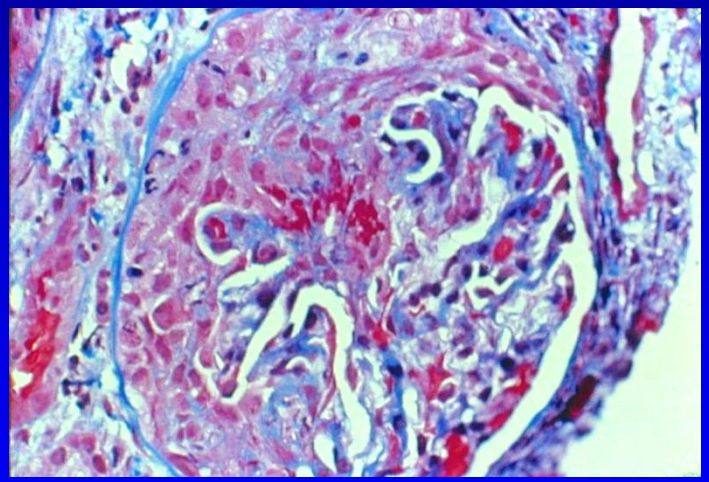
kidneys

Microscopic Polyangiitis



vasculitis

Differs from GPA in lacking granulomatous inflammation

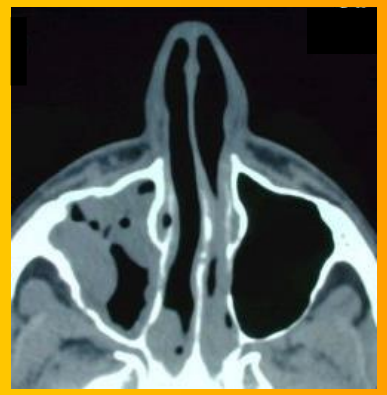


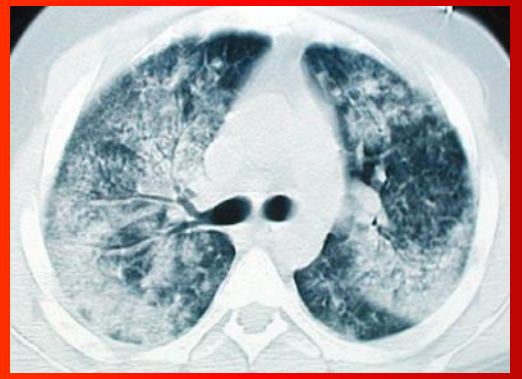
glomerulonephritis

Current treatment approaches for GPA and MPA are similar
(but there are adjunctive measures that are specific for GPA)

Spectrum of Disease Severity in ANCA-Associated Vasculitis

Non-Severe





Severe

- Sinonasal disease
- Oral mucosa
- Skin
- Joint
- Conductive hearing
- Lung – without respiratory compromise

- Glomerulonephritis
- Alveolar hemorrhage
- CNS
- Mononeuritis multiplex
- Pericarditis
- Vision threatening scleritis

Impacts treatment decisions

ANCA-Associated Vasculitis – Goals of Treatment

When weighing any therapeutic approach
it is important to consider how does it address the goals of treatment

- Patient survival
- Induce remission of active disease

  Remission - absence of disease activity
- Avoid disease relapse

  Relapse - return of disease activity after remission
- Minimize therapeutic toxicity
- Reduce the risk of permanent organ damage
- Optimize patient quality of life

Treatment of ANCA-Associated Vasculitis
Historical Perspective

Untreated disease

Walton. BMJ 1958;2(5091):265

- Median survival time 5 months

Glucocorticoids alone

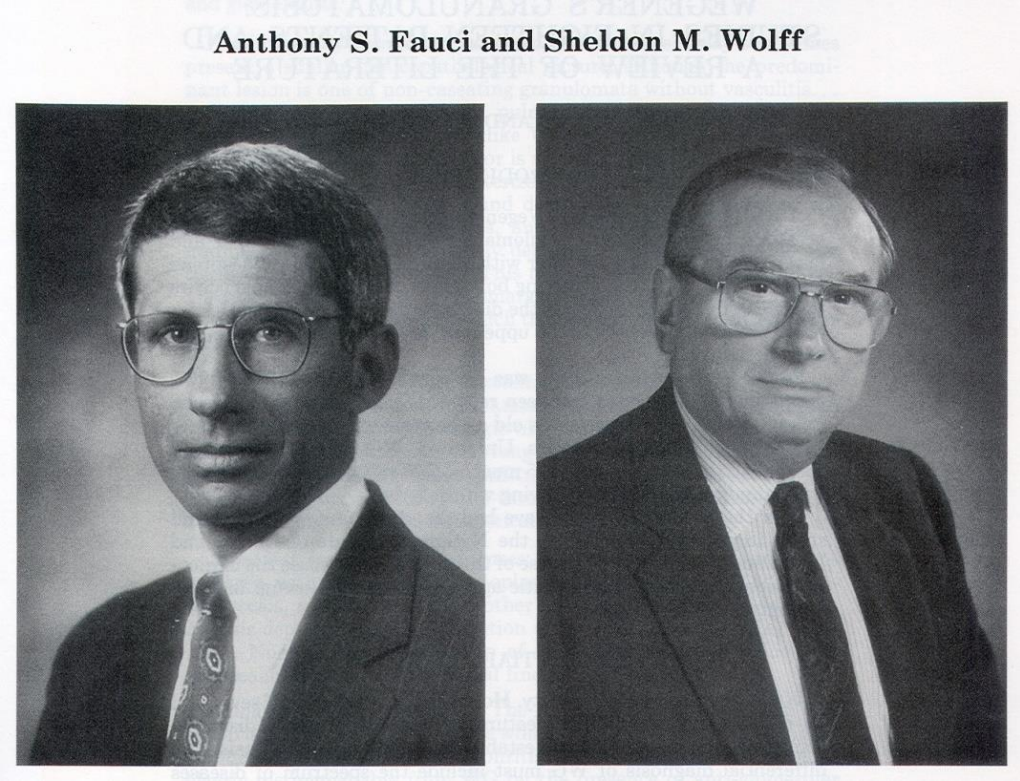
Hollander & Manning. Ann Int Med 1967;67:393

- Median survival time 12.5 months

Daily cyclophosphamide and prednisone

*Fauci & Wolff. Medicine 1973:*52:535

- Remission in 12 / 14 patients

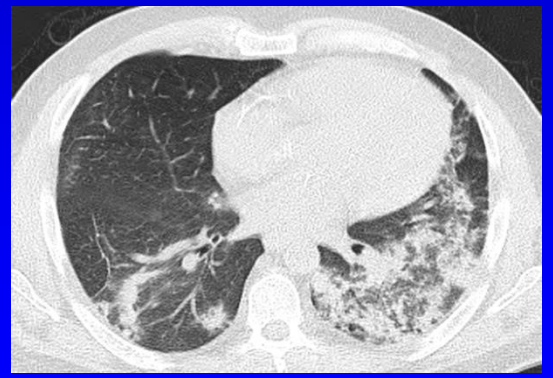


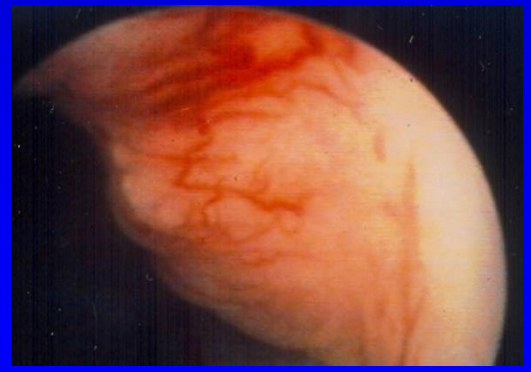
Cyclophosphamide – Experience Gained Over Time

Fauci & Wolff. Medicine 1973, Fauci et al. Ann Int Med 1983;98:76, Hoffman et al. Ann Int Med 1992;116:488

	Fauci 1983	Hoffman 1992
Mean follow-up	51 months (+ 4.3)	96 months
Rate of remission induction	93%	75%
Relapse rate	32%	50%
Cystitis	34%	43%
Serious infection	2%	46%
Bladder cancer	0%	2.8%

Pneumocystis jirovecii

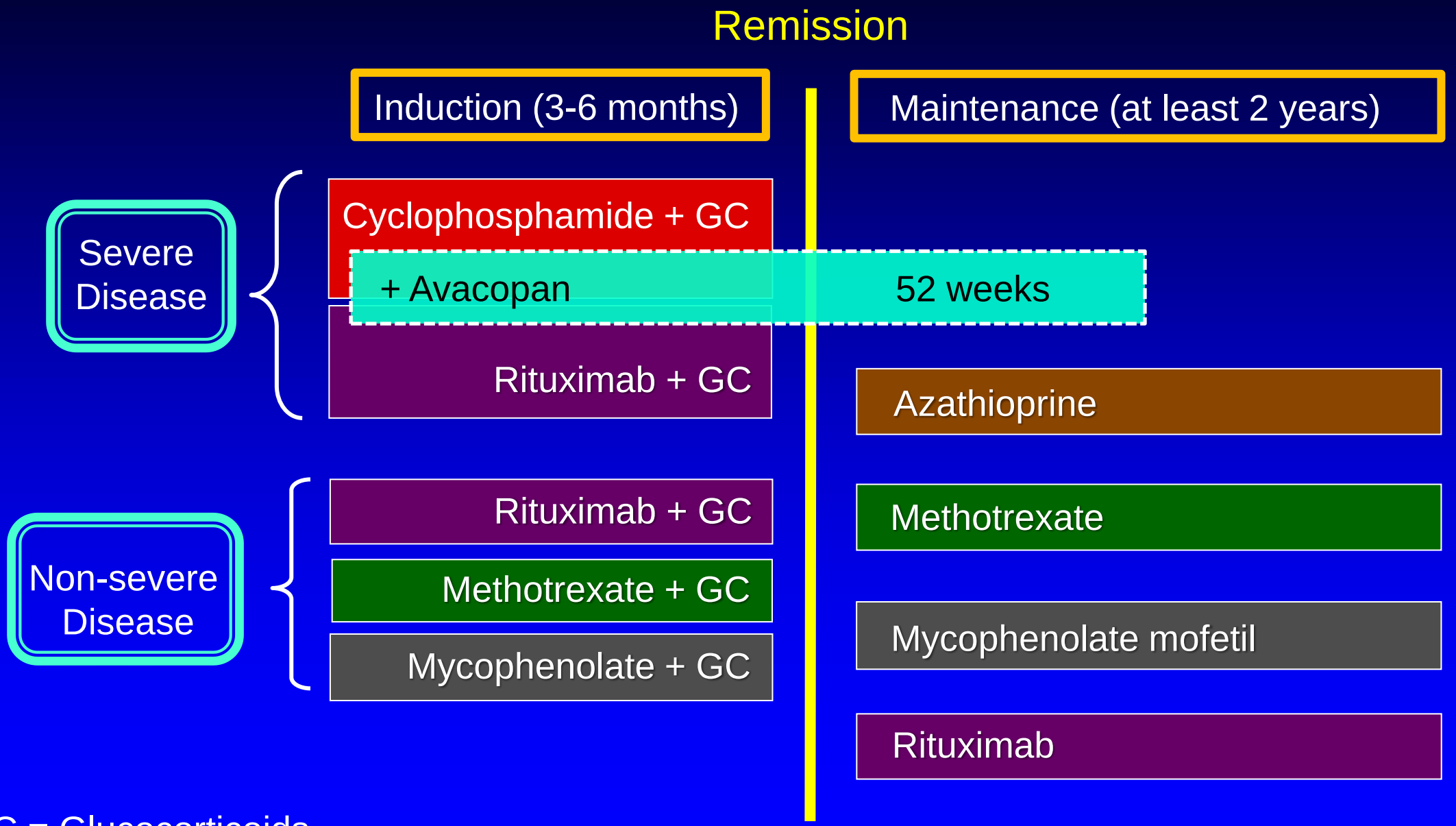




Transitional Cell Carcinoma

Cyclophosphamide – effective but additional approaches were needed

ANCA-Associated Vasculitis – Treatment Options In 2025



GC = Glucocorticoids

ANCA-Associated Vasculitis

Published Treatment Recommendations / Guidelines

2021 American College of Rheumatology (ACR) / Vasculitis Foundation

Chung et al. Arthritis Rheumatol 2021;73:1366

2022 European Alliance of Associations for Rheumatology (EULAR)

Hellmich et al. Ann Rheum Dis 2024;83:30

2024 Kidney Disease Improving Global Outcomes (KDIGO)

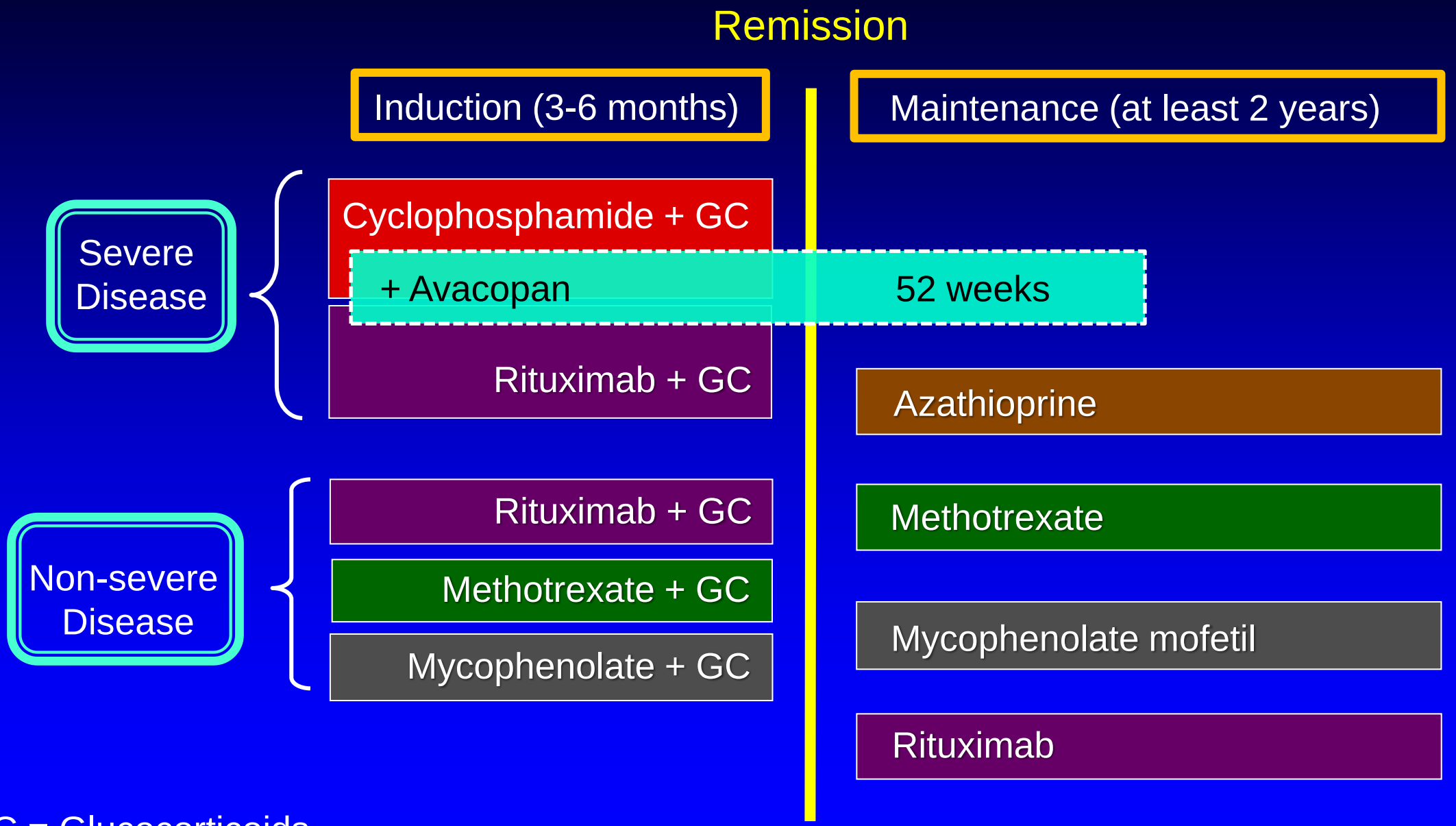
Floege et al. Kidney Int 2024;105:447 (https://kdigo.org/guidelines/gd/)

Guideline Comparison

	ACR/VF 2021	EULAR 2022	KDIGO 2024
Induction – Non-Severe *	MTX over RTX, CYC, AZA, MMF, GC alone	RTX over MTX, MMF	Not addressed
Induction – Severe * Creatinine < 3.4 mg/dL	RTX over CYC	RTX over CYC	RTX or CYC
Induction – Severe * Creatinine ≥ 3.4-5.7 mg/dL	RTX over CYC No PLEX	RTX over CYC Consider PLEX	Consider PLEX
Induction – Severe * Creatinine ≥ 5.7 mg/dL			Creatinine ≥ 4.0 mg/dL RTX + CYC or CYC
Maintenance after severe	RTX over MTX, AZA	RTX MTX, AZA alternatives	RTX or AZA
* Combined with glucocorticoids			

Differing opinions exist in a number of areas of management

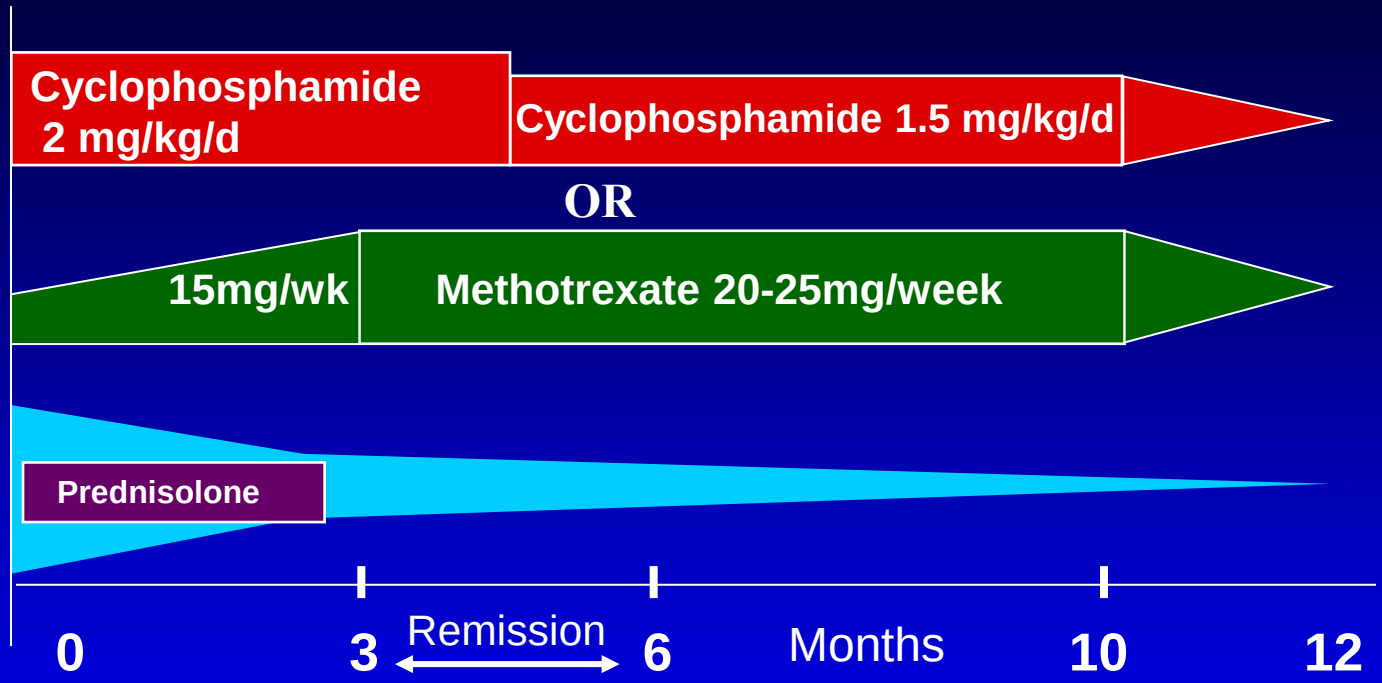
ANCA-Associated Vasculitis – Treatment Options In 2025



GC = Glucocorticoids

Non-Severe Disease – Cyclophosphamide vs Methotrexate

deGroot et al. Arthritis Rheum 2005;52:2461



100 patients

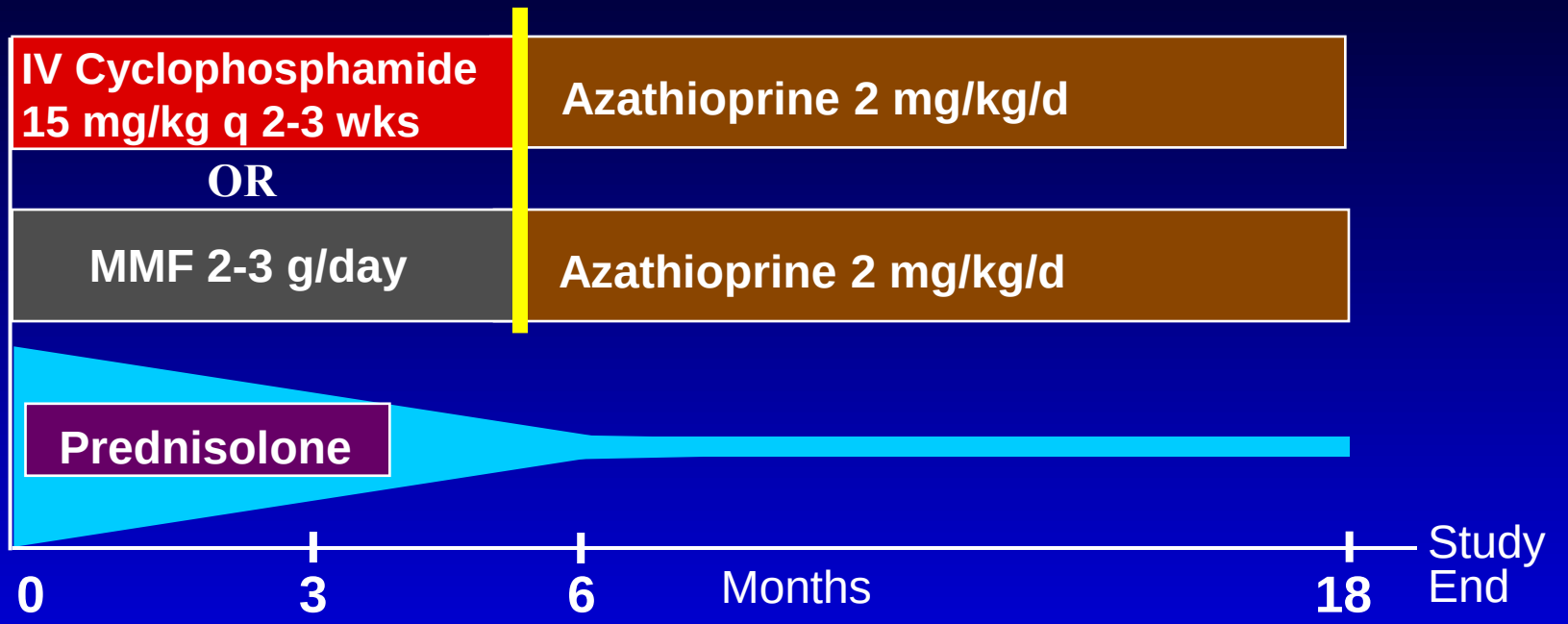
Induction of remission within 6 months

Methotrexate	90%
Cyclophosphamide	93%

Methotrexate is not inferior to cyclophosphamide for remission induction of non-severe disease in eligible patients

Non-Severe Disease – Cyclophosphamide vs Mycophenolate

Jones et al. ARD 2019;78:399



140 patients

Induction of remission by 6 months

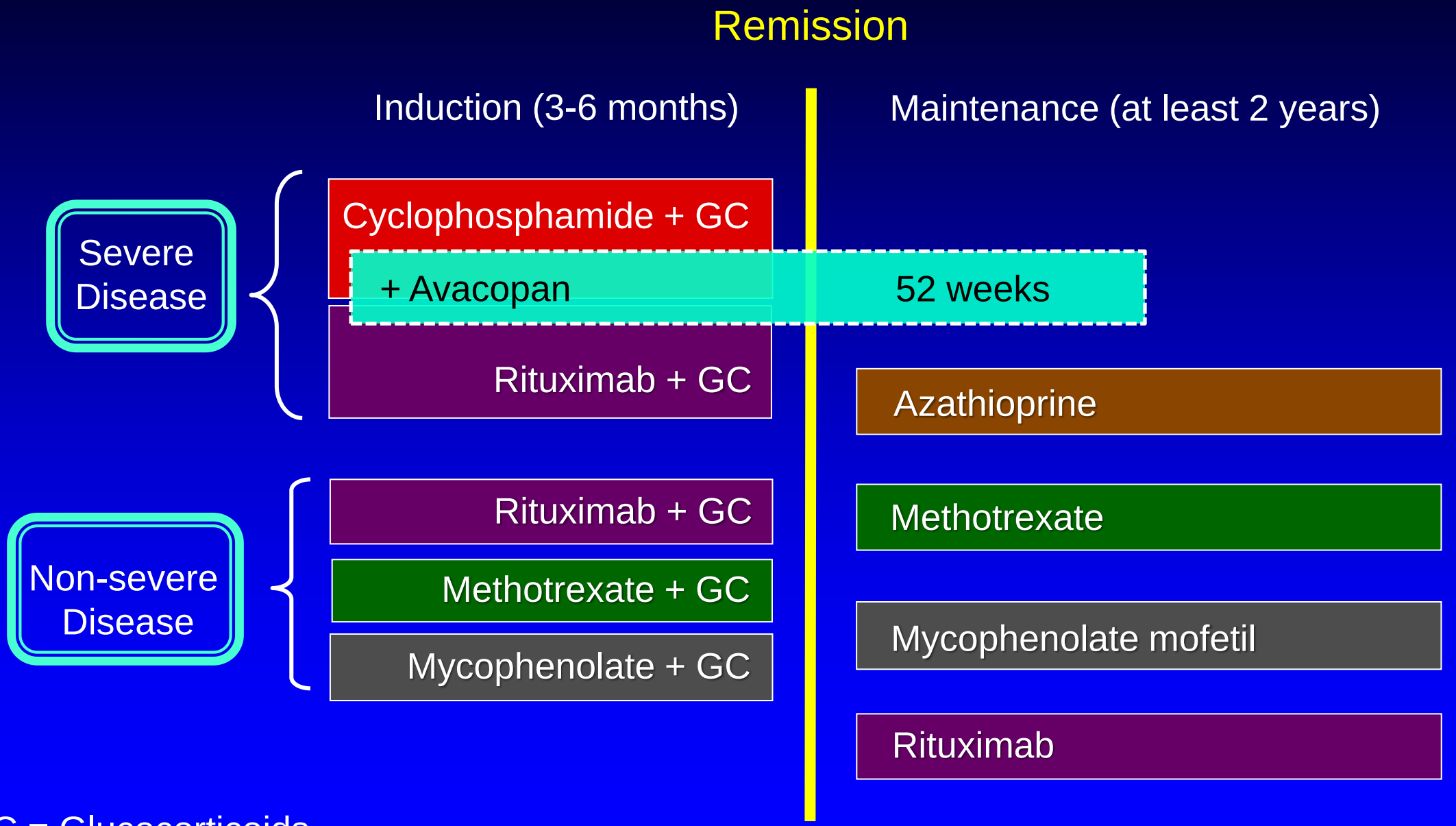
Mycophenolate mofetil	67%
Cyclophosphamide	61%

Relapse: MMF 33%, CYC 19% (p=0.049)
Serious adverse events: MMF = CYC
Serious infections: MMF = CYC

CYC affects fertility but MMF teratogenic

MMF is not inferior to cyclophosphamide for remission induction of non-life threatening disease but has a higher relapse rate

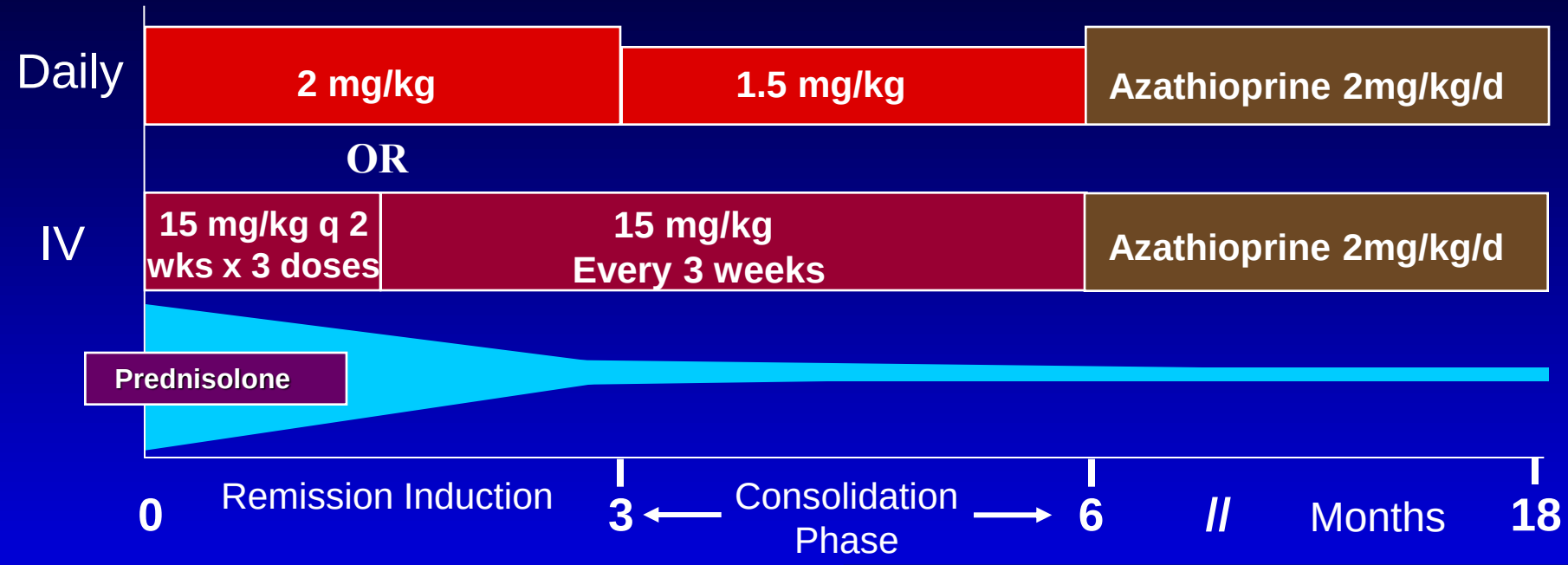
ANCA-Associated Vasculitis – Treatment Options In 2025



GC = Glucocorticoids

Daily versus Intermittent (IV) Cyclophosphamide for Remission Induction

deGroot et al. Ann Int Med 2009;150:670, Harper et al. ARD 2012;71:955



149 patients

- Time to remission: IV=PO, median 3 mo
- Long term relapse: IV 40%, PO 21% (p=0.03)
- Total CYC dose: IV < PO (similar at 3 mo)
- Leukopenia: IV < PO (PO occurred after mo 2)

Issues to consider

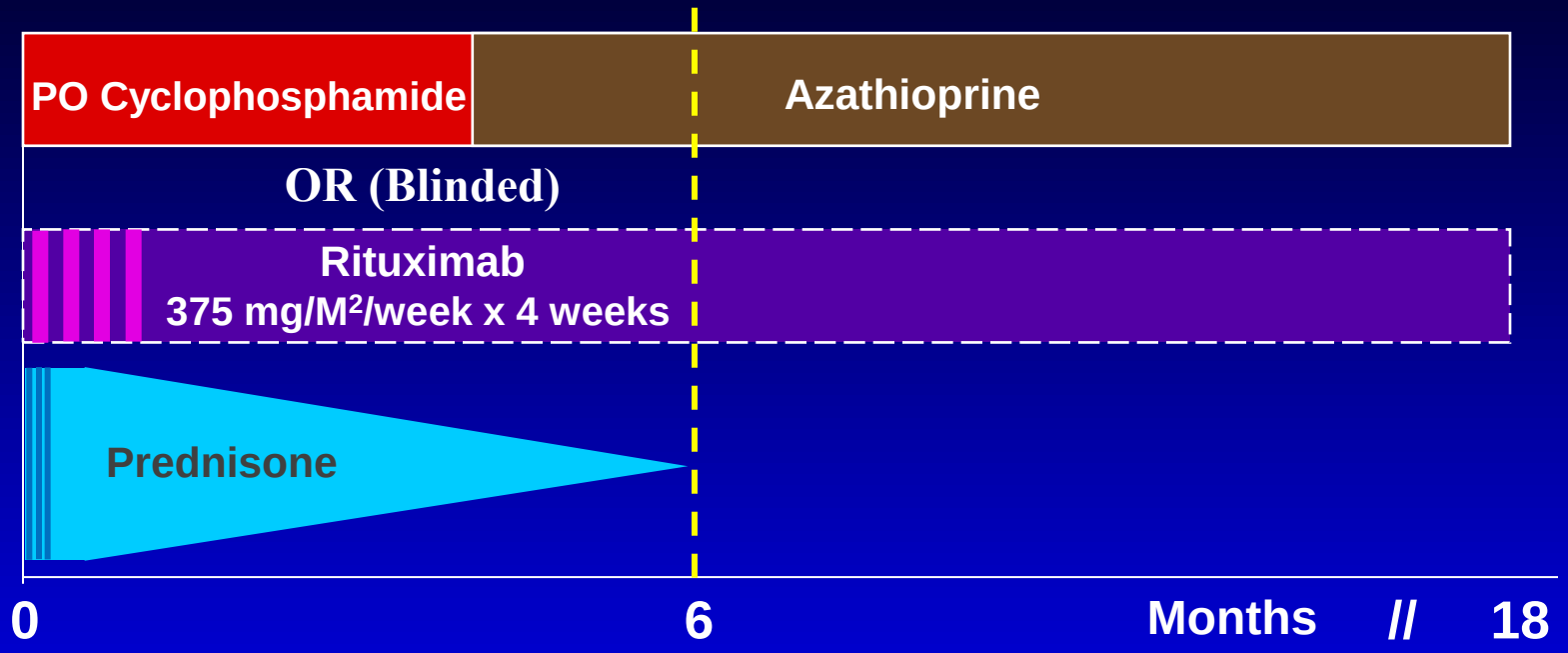
- Consolidation phase
- CBC frequency (wbc drops over time)
  - – IV days 10, 14, before pulse;
  - – PO QW x 1 mo, QOW x 1 mo, then monthly

IV CYC - effective but not superior to daily CYC – higher relapse rate

When using PO CYC – aim for 3-4 months, with q 1-2 week CBC

Cyclophosphamide vs Rituximab for Remission Induction (RAVE)

Stone et al. NEJM 2010; 363:221, Specks et al. NEJM 2013;369:417



Significant exclusions:
- creatinine > 4.0 mg/dL
- mechanical ventilation

Primary Endpoint = in remission and off prednisone at 6 months

197 ANCA (+) GPA or MPA

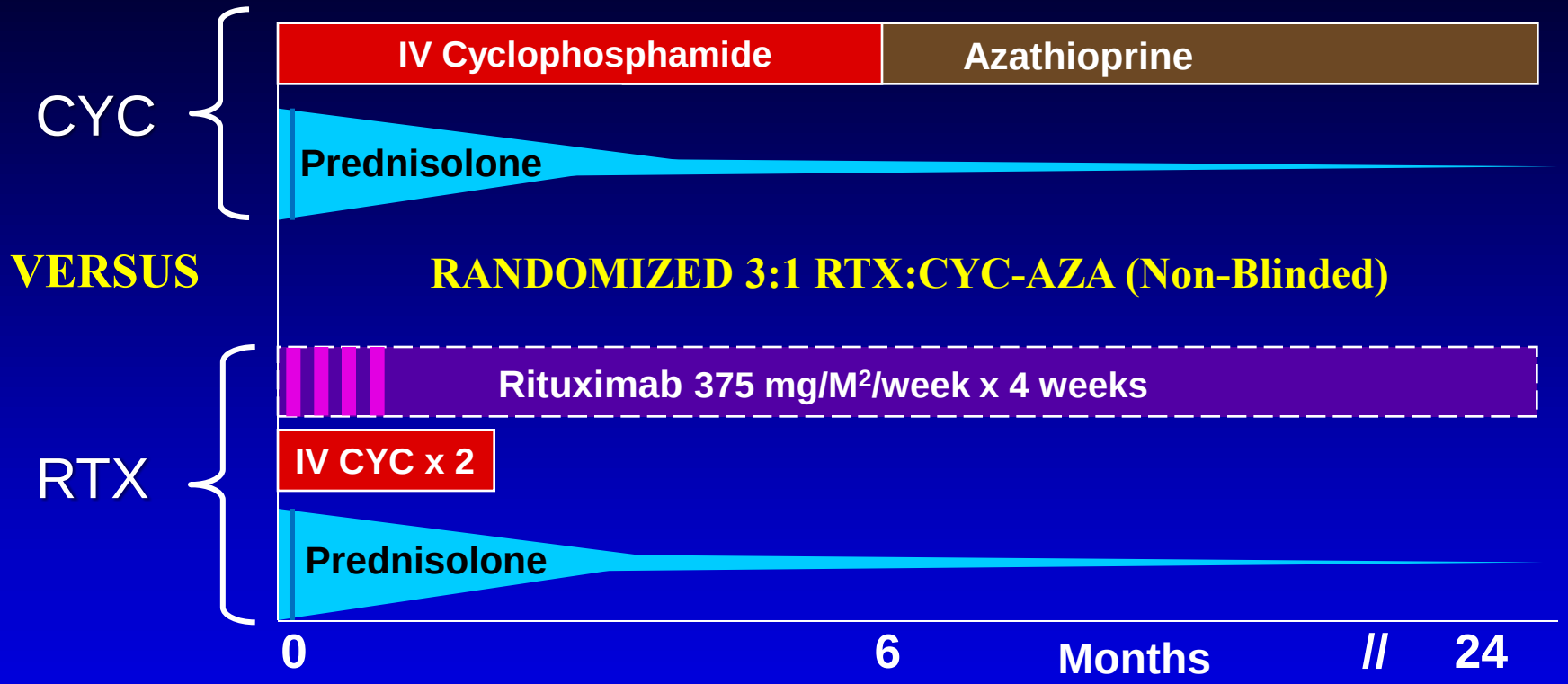
Meeting primary endpoint
All patients: RTX 64%, CYC 53% (P<0.001)
Relapsing patients: RTX 67%, CYC 42%

Rate of adverse events: RTX = CYC
Infections: RTX = CYC
Mortality rate: 2% (1 RTX, 2 CYC)

For remission induction, rituximab is as effective as cyclophosphamide
This was the basis for FDA approval of rituximab for GPA/MPA in April 2011

Cyclophosphamide vs Rituximab for Remission Induction (RITUXVAS)

Jones et al. NEJM 2010; 363:211



Primary Endpoint = sustained remission (BVAS=0 for 6 months)

44 ANCA (+) GPA or MPA, new dx

Hypothesis: RTX better than CYC
Primary endpoint: RTX 76%, CYC 82%

Rate of adverse events: RTX = CYC

Mortality rate: 18% (6 RTX, 2 CYC)
- Median age 68, 20% dialysis
- eGFR: RTX 20 ml/min, CYC 12 ml/min

Rituximab was not superior to cyclophosphamide but appeared to be as effective

What About Combined Cyclophosphamide + Rituximab ?

There have been a number of publications examining this regimen:

Cortezar et al. Kidney International Reports 2018; 3:394
McAdoo et al. Nephrol Dial Transplant 2019; 34:63
Gulati et al. Kidney International 2021; 100:1316
Pepper et al. Rheumatol 2021; 58:260

Main rationale: Reduction of glucocorticoids

Limitations/concerns:

- All are non-standardized (except RITUXVAS), most are retrospective, single-center
- Small sample sizes with short length of follow-up
- Variable: disease severity, duration of glucocorticoids
- Hypogammaglobulinemia 6-22%
- Serious infection 10-37%
- Death 3-18%

Data with combined cyclophosphamide and rituximab remains limited, has not been proven more effective than use of each agent alone, and raises concerns for toxicity

Rituximab or Cyclophosphamide for Remission Induction of Severe AAV ?

Settings which favor use of rituximab*:

- Relapsing severe disease
- Newly diagnosed patients who are: younger (fertility) or older (poor tolerance of CYC)
- Patients with leucopenia, thrombocytopenia
- Patients with urinary retention
- Patients with malignancy history
- Patients with infections

* ACR/VF guidelines conditionally recommend rituximab over cyclophosphamide for remission induction of active severe disease

Settings in which to consider cyclophosphamide*:

- Severe disease with intolerance to rituximab
- Worsening severe disease despite rituximab
- Fulminant disease (RPGN creatinine > 4.0 mg/dL, mechanical ventilation) ?

Relapse After Remission Induction in ANCA-Associated Vasculitis

Cyclophosphamide *(Hoffman et al. Ann Int Med 1992;116:488)*

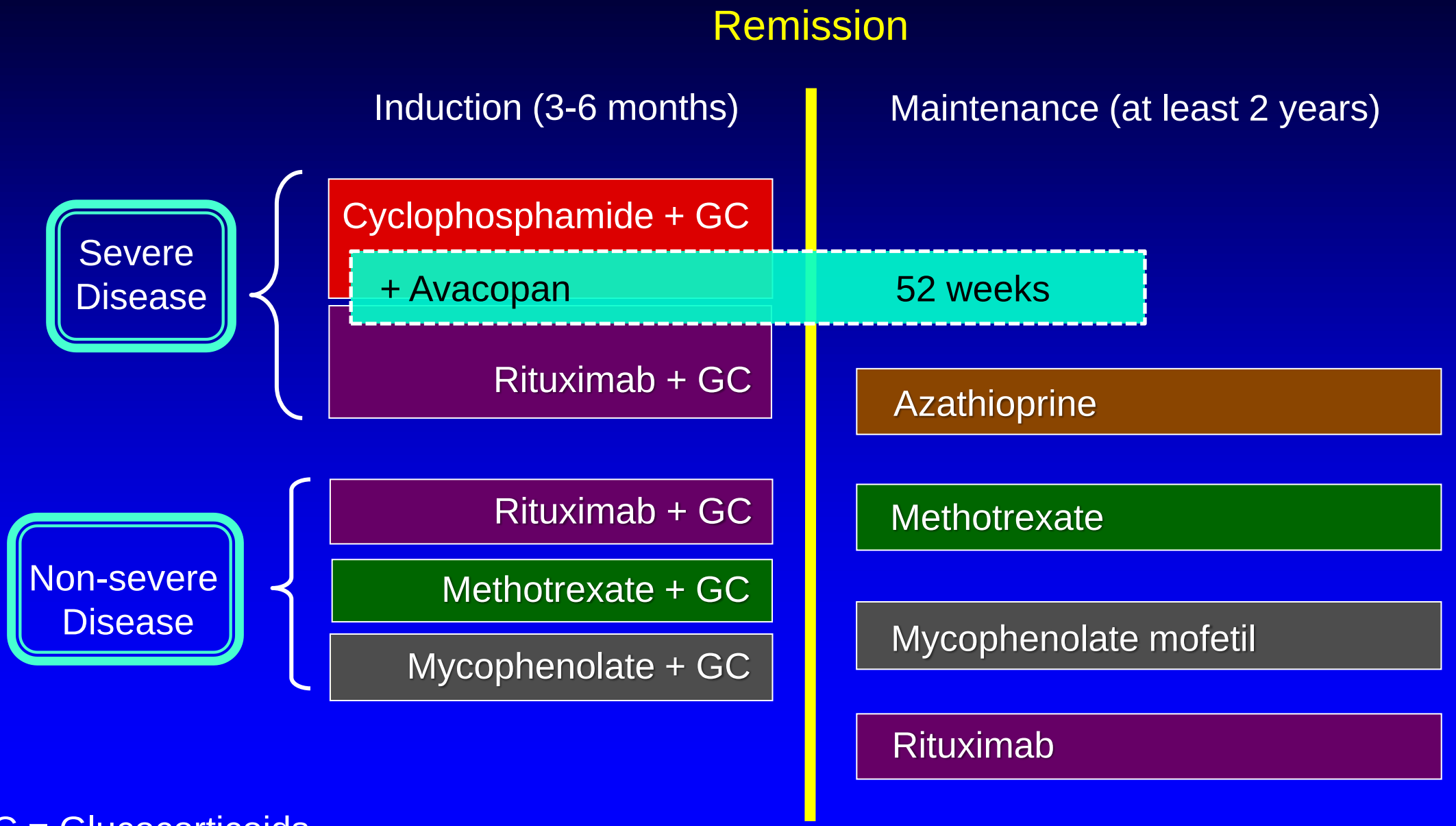
- 50-70% relapse after achievement of remission

Rituximab *(Specks et al. N Engl J Med 2013;369:417)*

- No difference in single course RTX vs CYC/AZA - 30% relapse within 1 year

Relapses can occur after either cyclophosphamide or rituximab such that remission maintenance needs to be considered in every patient

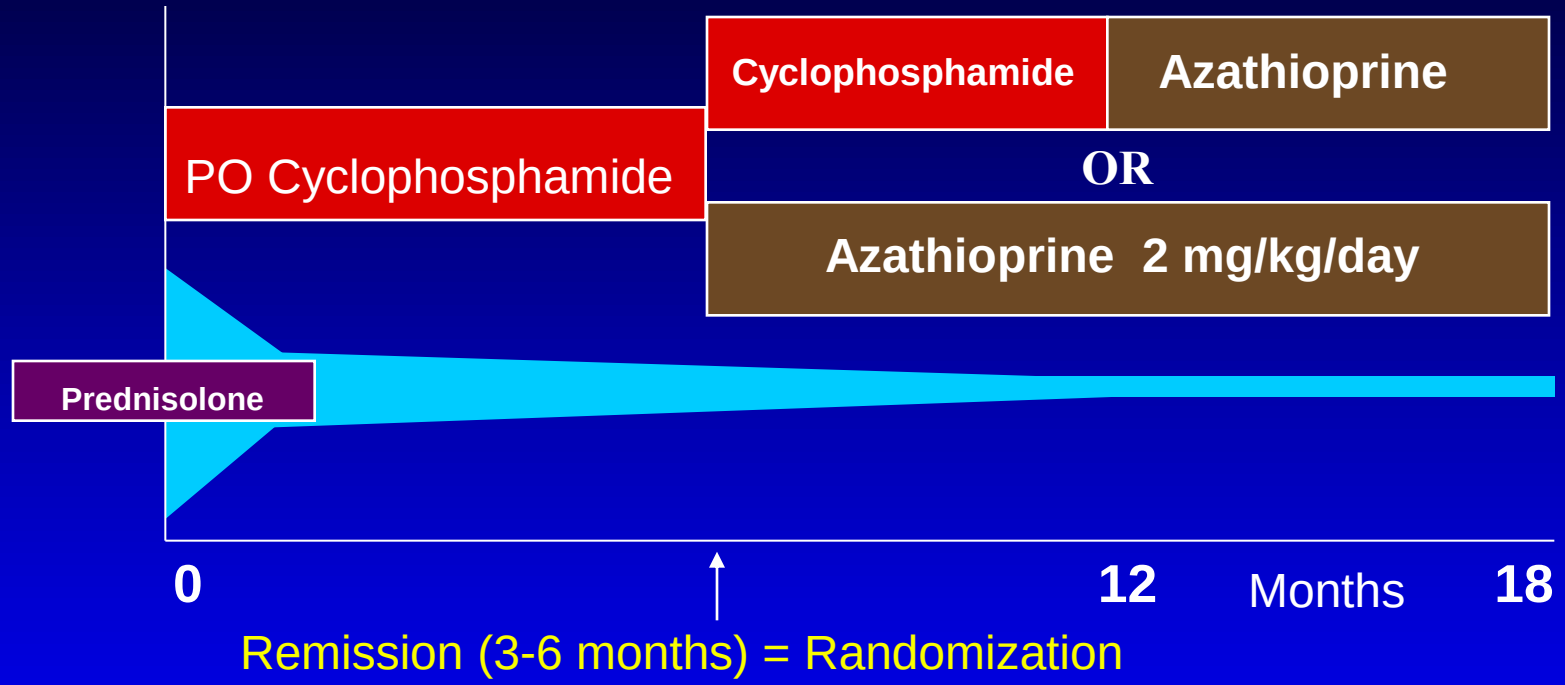
ANCA-Associated Vasculitis – Treatment Options In 2025



GC = Glucocorticoids

Cyclophosphamide vs Azathioprine for Remission Maintenance

Jayne et al. NEJM 2003; 349:36



155 patients

95% Survival
93% Remission

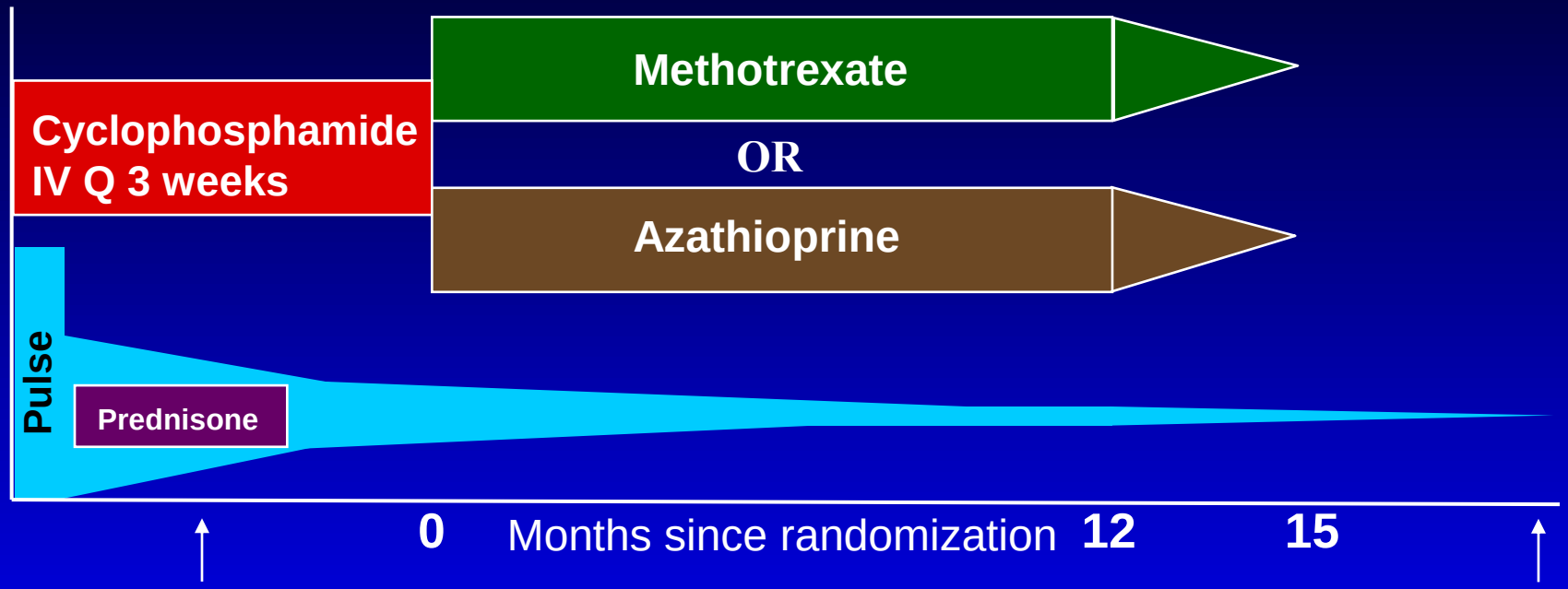
Relapse at 18 months

Cyclophosphamide	14%	P=0.65
Azathioprine	16%	

Azathioprine maintained remission without an increase in relapse rate

Methotrexate vs Azathioprine for Remission Maintenance

Pagnoux et al. NEJM 2008;359:2790



159 patients – 126 (79%) Remission

Toxicity

Methotrexate	46%	P=0.29
Azathioprine	56%	

Relapse

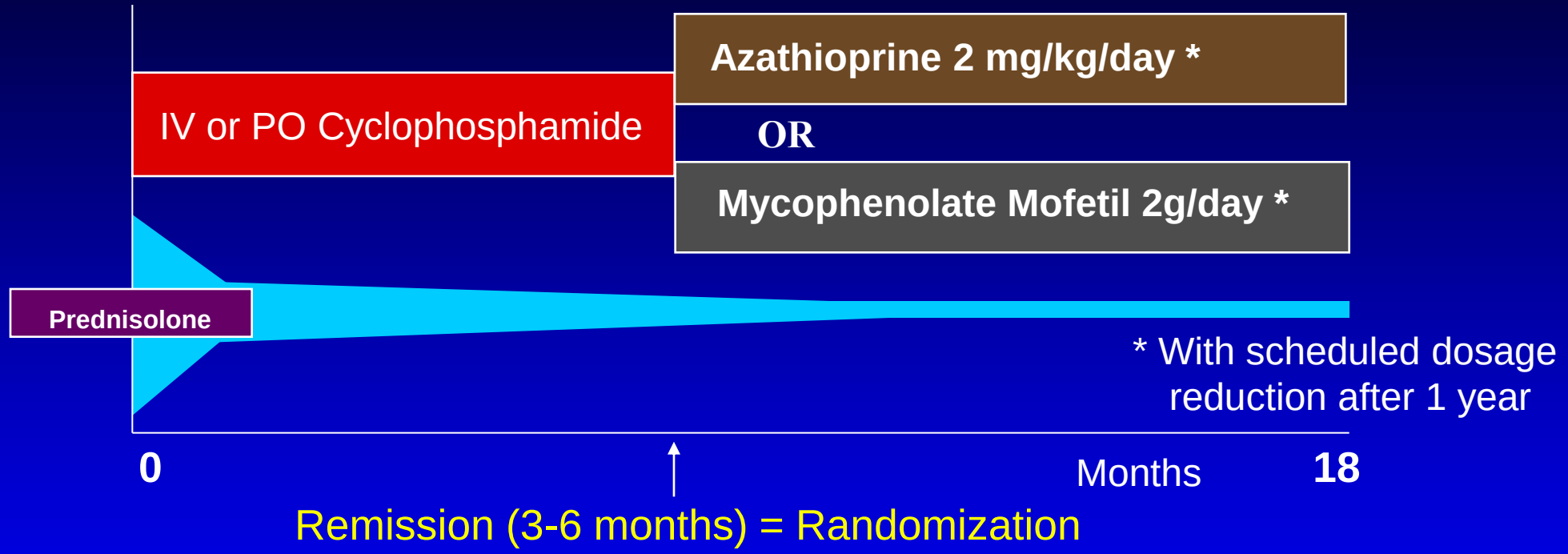
Methotrexate	36%	P=0.71
Azathioprine	33%	

73% of relapses were after drug was stopped

Azathioprine and methotrexate are comparable for remission maintenance

Mycophenolate Mofetil (MMF) vs Azathioprine for Remission Maintenance

Hiemstra et al. JAMA 2010; 304:2381



Remission (3-6 months) = Randomization

156 patients

Relapse

Mycophenolate	55%	P=0.03
Azathioprine	38%	

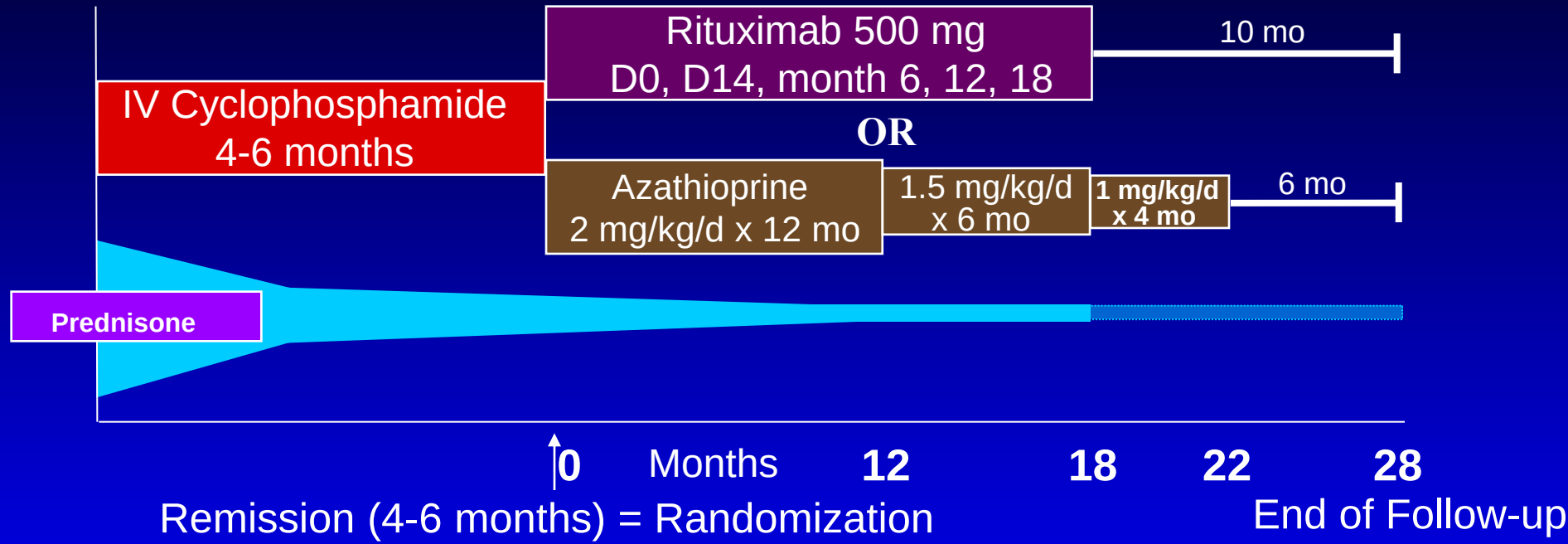
Toxicity (severe adverse events)

Mycophenolate	7.5%	P=0.12
Azathioprine	16%	

MMF was less effective than azathioprine for maintaining remission

Remission Maintenance with Rituximab vs Azathioprine (MAINRITSAN)

Guillevin et al. NEJM 2014;371:1771, Terrier et al. ARD 2018; 77:1150



115 patients

Major relapse Month 28

RTX 5%
AZA 29%
P=0.002

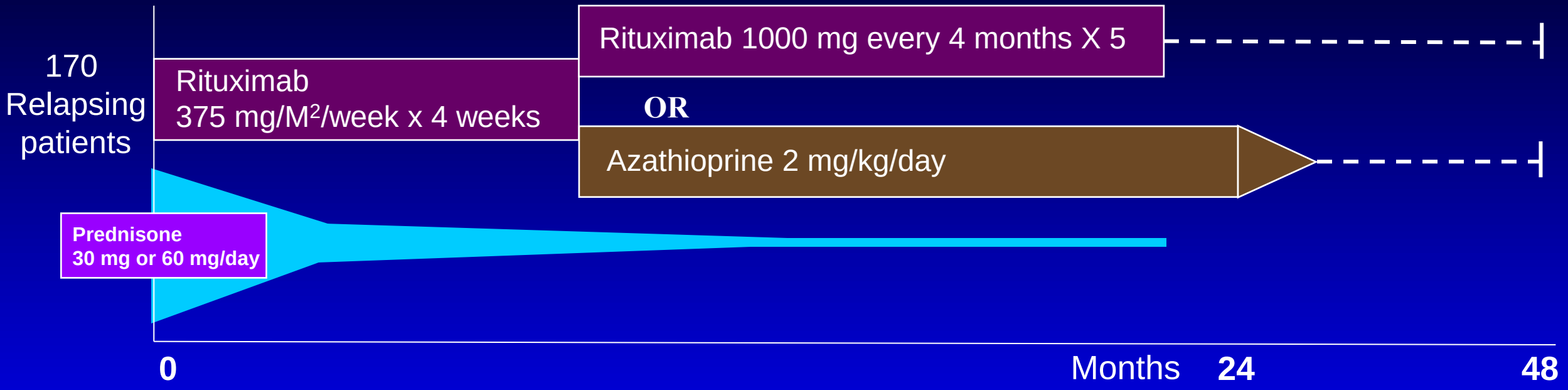
Month 60 Follow-up

- RTX still superior – but 42% had relapsed

Rituximab was more effective than azathioprine to maintain remission
Relapses occurred after treatment was stopped

Remission Maintenance with Rituximab vs Azathioprine (RITAZAREM)

Smith et al. ARD 2023;82:937



Relapse	At 24 months		At 48 months	
Rituximab	15%	P < 0.001	50%	P < 0.001
Azathioprine	38%		78%	

Similar rate of serious adverse events

IgG < 5 g/L RTX 42%, AZA 31%

Rituximab was more effective than azathioprine to maintain remission

Relapses occurred with both once treatment was stopped

RTX 1000 mg/every 4 months did not have a sustained effect after discontinuation

Choice of Agent for Remission Maintenance Therapy

Rituximab*

- Rituximab for remission maintenance has a lower rate of relapse than azathioprine
- Main problem: Relapses occur after rituximab is stopped
- Duration of rituximab treatment remains unclear
- Concerns remain for toxicity with long-term use – especially hypogammaglobulinemia
  - Check IgG level before treatment and 1-2 times per year
- Impact on vaccine response

* ACR/VF guidelines conditionally recommend rituximab over azathioprine or methotrexate for remission maintenance

Do conventional agents (AZA, MTX, MMF) still have a place in maintenance* ?

- Yes – after risks and benefits are weighed
- Disadvantage: Higher rate of relapse compared to rituximab
  - Low but present risk long-term: malignancies, bone marrow fatigue, hepatic (some agents)
- Advantage: Well-known therapies with an established long-term side-effect profile

Duration of Remission Maintenance Therapy

Most trials in ANCA-associated vasculitis are based on 18-24 months of maintenance (but this is not a 24-month disease)

With either rituximab or conventional agents - relapse rate higher off treatment

Maintenance beyond 24 months is appropriate in many instances

- Duration of maintenance should be decided with the patient weighing individual factors:
  - Relapse history
  - Presence of organ damage
  - Toxicity (influenced by choice of maintenance agent)
  - Patient preferences, compliance, family planning

- With rituximab - beyond 24 months discuss options with patient:
  - Continue every 6 months vs lengthen time between infusions vs stop and monitor

Plasma Exchange (PLEX) in ANCA-Associated Vasculitis

Plasma exchange has been used in fulminant AAV

Rapidly Progressive Glomerulonephritis (RPGN)

MEPEX trial *(Jayne et al. JASN 2007;18:2180, Walsh et al. Kid Int 2013;84:397)*

- 137 patients, (+) renal biopsy, creatinine > 5.8 mg/dL
- All received CYC, randomized to receive IV methylprednisolone or PLEX
- At 3 months those alive and off dialysis - 49% MP, 69% PLEX (P=0.02)
- Longer term results found no effect of PLEX on mortality, ESKD

Alveolar hemorrhage (DAH)

Klemmer et al. Am J Kid Dis 2003;42:1149

- Retrospective survey of 20 patients with DAH
- 100% improved – but all also received aggressive systemic immunosuppression

Cartin-Ceba et al. A&R 2016;68:1467

- Retrospective survey and literature review (total 172 patients)
- PLEX did not impact resolution of DAH or survival

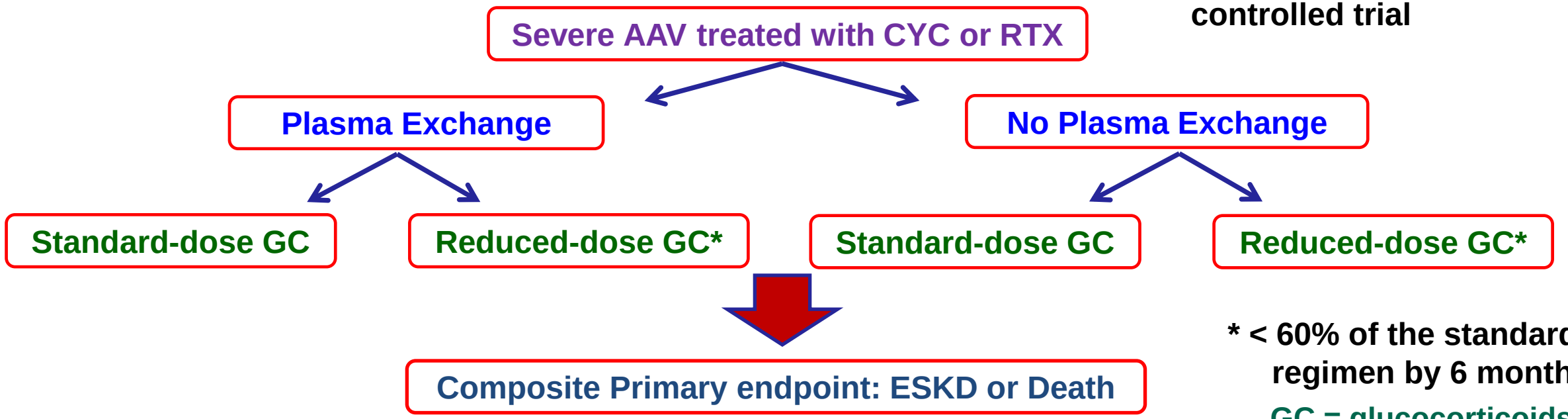
Supported the need to more definitively establish the efficacy of plasma exchange

Plasma Exchange (PLEX) in ANCA-Associated Vasculitis

Walsh et al. NEJM 2020;382:622

PEXIVAS

2x2 factorial randomized controlled trial



*** < 60% of the standard regimen by 6 months**

GC = glucocorticoids

- Enrolled patients had to have either severe renal involvement or diffuse alveolar hemorrhage (DAH)
- 704 patients - 98% with renal involvement, 27% with DAH (8% had severe hemorrhage)

Plasma Exchange (PLEX) in ANCA-Associated Vasculitis

Walsh et al. NEJM 2020;382:622

- Primary endpoint: Composite endpoint of ESKD or death in AAV
  - 28% PLEX vs 31% no PLEX (Hazard Ratio 0.86; 95% CI 0.65-1.13; P=0.27)
  - No difference in subgroup analyses or secondary endpoints
    - Creatinine ≥ 5.7 mg/dL (Hazard Ratio 0.77; 95% CI 0.53-1.11)
    - Alveolar hemorrhage, pO2 ≤ 85% (Hazard Ratio 0.67; 95% CI 0.28-1.64)

- Limitations:
  - Wide confidence interval that crosses 1.0
  - Secondary analyses are subject to type 2 error

- Strength:
  - Large study that was powered to look at the primary outcome

Use of plasma exchange did not reduce the incidence of ESKD or death in AAV

Plasma Exchange (PLEX) in ANCA-Associated Vasculitis

Walsh et al. BMJ 2022;376:e064604

- Meta-analysis of 9 randomized trials, 1060 participants (1980-2020)
- PLEX had no impact on all-cause mortality, Relative risk 0.90 (95% CI 0.64-1.27)
- PLEX reduced the risk of ESKD at 12 months, Relative risk 0.62 (95% CI 0.39-0.98)
  - Low risk (Creatinine $\leq$ 2.3 mg/dL) – risk reduction 0.08%
  - Low-moderate risk (Creatinine 2.3-3.4 mg/dL) – risk reduction 2.1%
  - Moderate-high risk (Creatinine 3.4-5.7 mg/dL) – risk reduction 4.6%
  - High risk (Creatinine > 5.7 ml/dL) – risk reduction 16.0%
- PLEX increased the risk of serious infection at 12 months, Relative risk 1.27 (95% CI 1.08-1.49)

- Strength: Meta-analysis
- Limitation: Trials that were included varied greatly

Plasma Exchange (PLEX) in ANCA-Associated Vasculitis

- Where is plasma exchange recommended ?
  - Dual positive anti-GBM and ANCA-associated vasculitis
- Active glomerulonephritis – data remains controversial
  - Largest randomized trial: PLEX did not impact outcome of death+ESKD, including by subgroups
  - Meta-analysis suggests risk reduction for ESKD in those with Creatinine $\geq$ 5.7 ml/dL but no decrease in mortality and increased infection
  - Decision about use needs to balance uncertain benefit against increased risk
- Alveolar hemorrhage – data does not support routine use
  - Fulminant disease worsening on maximal support despite current treatment ?
- If plasma exchange is performed:
  - Do not PLEX for at least 48 hours after rituximab

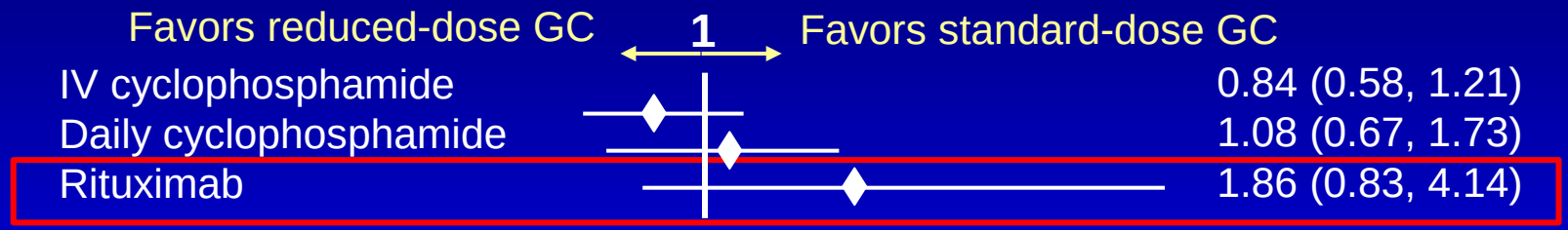
Reduced-Dose Glucocorticoids

Walsh et al. NEJM 2020;382:622

Reduced-dose glucocorticoids in the PEXIVAS trial

- Primary endpoint: Composite endpoint of ESKD or death in AAV
  - 28% reduced-dose GC vs 26% standard-dose GC (met criterion for non-inferiority)
- Serious infections at 1 year were less common in reduced-dose GC

Subgroup analysis:
Induction immunosuppression



Nagle et al. ARD 2025;84:319

- Retrospective study 234 patients
- Primary endpoint: Composite ESKD, death, disease progression, relapse within 12 months
  - 33% reduced-dose GC vs 19% standard-dose GC (p=0.01)
  - Creatinine ≥ 300 µmol/L received reduced-dose GC were more likely to achieve primary outcome
- Reduced-dose GC was not associated with a higher rate of ESKD or death
- No difference in serious infections at 1 year between reduced-dose GC and standard-dose GC

Use of reduced-dose GC can be effective and reduce infection risk
Potential exists for individual response differences that may require standard-dose schedules

Avacopan

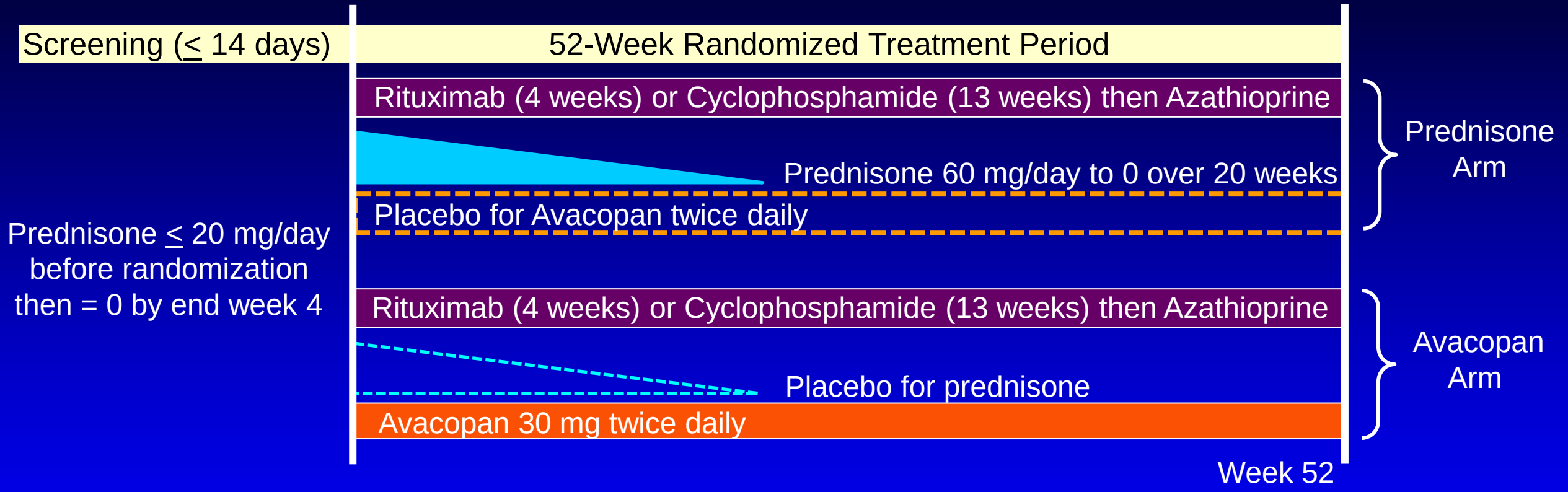
Background:

- Avacopan is a selective oral small molecule inhibitor of the complement 5a receptor (C5aR)
- C5a and C5aR may play a role in AAV by driving neutrophil activation
- In an AAV animal model, C5aR knock-out or antagonism stopped the development of vasculitis (*Xiao et al. J Am Soc Nephrol 2014;25:225*)

Two Phase II studies of avacopan in AAV

- CLASSIC *(Merkel et al. ACR Open Rheumatol 2020;2:662)*
  - Avacopan added to standard of care (CYC or RTX + prednisone 60 mg/day)
  - No difference in the rate of serious adverse events/adverse events
- CLEAR *(Jayne et al. J Am Soc Nephrol 2017;28:2756)*
  - Avacopan + CYC or RTX and (prednisone 60 mg/day vs 20 mg/day vs 0 mg)
  - No difference in clinical response between the 3 prednisone groups

Randomized Trial of Avacopan *(Jayne et al. NEJM 2021;384:599)*



- 330 newly diagnosed or relapsing GPA or MPA, (+) PR-3 or MPO ANCA, moderate/severe active disease
- Rituximab induction: 64.5% avacopan, 65.2% prednisone
- Organ involvement: 81% renal, 43% lung, 44% ENT, 20% eye/mucous membrane
  - eGFR ≤ 20 ml/min/1.73 M^2: 16% avacopan, 14% prednisone

Randomized Trial of Avacopan *(Jayne et al. NEJM 2021;384:599)*

	Avacopan (N=166)	Prednisone (N=164)	
Week 26 remission	120 (72%)	115 (70%)	P < 0.0001 (non-inferiority)
Week 52 remission	109 (66%)	90 (55%)	P < 0.0001 (non-inferiority) P = 0.0066 (superiority)
Serious adverse events	62 (37.3%)	64 (39%)	
Glucocorticoids during 52-weeks %, total dose, mean daily dose	87.3%, 1676 mg, 5 mg	100%, 3847 mg, 12.5 mg	

- Avacopan was non-inferior to prednisone for remission at Week 26
- Avacopan was superior to prednisone for sustained remission at Week 52

} Primary endpoints

- Safety in the avacopan and prednisone arms was similar
  - Main side effects: hepatotoxicity, infection
  - Metabolized by CYP3A4 - interaction with CYP3A4 inducers/inhibitors
- Glucocorticoids – less but not free
  - Use in the avacopan arm: 75% during screening, 87.3% during treatment period

Randomized Trial of Avacopan *(Jayne et al. NEJM 2021;384:599)*

Renal outcomes
(Cortazar et al. KI Reports 2023;8:860)

	↑ in eGFR ml/min/1.73 M^2 by Week 52		
	Avacopan	Prednisone	
Total renal population	7.3	4.1	P=0.029
eGFR ≤ 20 ml/min/1.73 M^2	16.1	7.7	P=0.003

- From Week 26 to 52 kidney function continued to improve with avacopan but not with prednisone
- Avacopan reverses decline in renal function to a greater degree than prednisone

Avacopan received FDA approval in October 2021

Patients with severe active GPA/MPA in combination with standard therapy including glucocorticoids

Current questions regarding avacopan:

- Will avacopan be equally effective for all disease features ?
- Duration of avacopan ? Current study stopped treatment at 52 weeks
- Use for non-severe disease ?
- Use for maintenance in place of other agents ?

Future Investigations

CD19 Chimeric antigen receptor (CAR)-T cells

- Murine study in MPO-AAV mouse model *(Lodka et al. ARD 2024;83:499)*
  - Found CD19 targeted CAR-T cells protect from ANCA-induced kidney injury

Obinutuzumab

- Anti-CD20 – associated with more profound, longer-lasting B cell depletion
- Report in 3 patients with anaphylaxis to rituximab *(Amudala et al. Rheumatol 2022;61:3814)*
- Being examined in 2 trials (NCT05376319, ISRCTN13069630)

Targeting B cell cytokines

- Anti-BAFF
  - Trial examining sequential rituximab and belimumab (NCT03967925)
- Anti-BAFF/Anti-APRIL
  - Povetacicept (NCT05732402)
  - Telitacicept (NCT05962840, NCT05965284)

Complement

- Exploration of further pathways

Conclusion: ANCA-Associated Vasculitis – 2025 and Beyond

In 2025, there are effective treatment options for ANCA-associated vasculitis that offer potential for long-term patient survival

Key issues of ongoing concern:

- Relapse
- Treatment toxicity
- Organ damage

What are future areas of discovery ?

- Continued understanding of pathogenesis – including genetics
- Biomarkers
  - Identifying relapse and those at risk of relapse
  - Guiding maintenance treatment – who needs what and when and for how long
- Understanding damage – can this be reversed ?