Caring for people with ANCA-associated glomerulonephritis and lupus nephritis

A guide to updated management guidelines

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Disclosures

- Consulting and/or research support (funds to institution)

  Visterra, Vifor, CSL-Seqirus, Sitala, Patrys

- Speaker – Vifor/CSL-Seqirus

- Chair, Australia and New Zealand Vasculitis Society

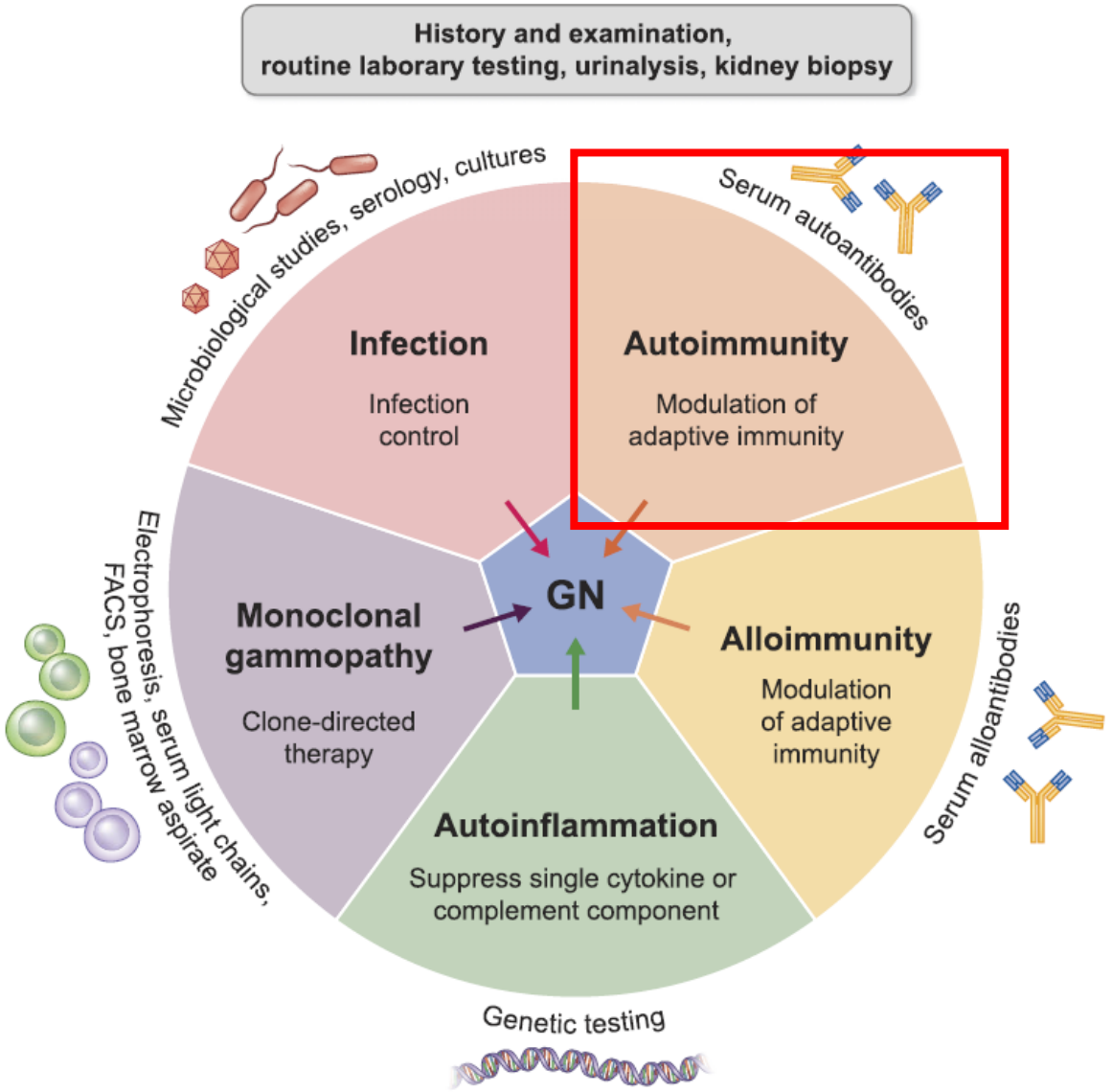
ANZVASC
Australia and New Zealand Vasculitis Society

- Funding: NHMRC Australia

Australian Government
National Health and Medical Research Council

NHMRC

Both ANCA-associated GN and lupus nephritis are autoimmune



Anders, Kitching, Leung, Romagnani. Nature Reviews Immunology 2023

Romagnani, Kitching, Leung, Anders. Nephrology, Dialysis, Transplantation 2023

Management: both ANCA-associated vasculitis and lupus nephritis

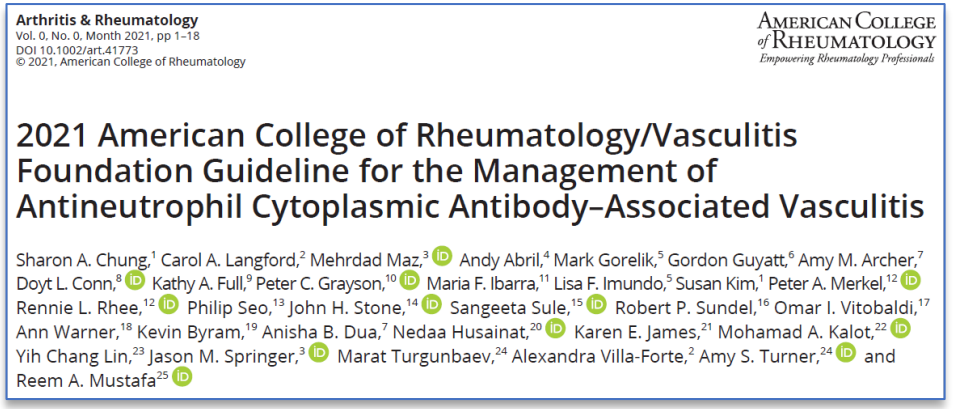
- Full assessment – these are systemic autoimmune diseases
  - Involvement of other organs and tissues
- Watch out for mimics and infection (especially in AAV)
- “Usually” a kidney biopsy
- Pre-immunosuppression evaluation – especially infection risk
- Adjunct and supportive therapies
  - CVS risk
  - BP/Na/prevent AKI
  - Bones
  - Contraception (most relevant to SLE)

AAV- Guidelines 2021-2024

Chung SA et al. ACR/VF Guidelines, 2021 Arthritis Rheumatol 2021 73:1366-1383

Hellmich B et al, EULAR Recommendations: Ann Rheum Dis 2024 Jan 2;83(1):30-47

KDIGO 2024: Kidney Int Volume 35 Issue 3S March 2024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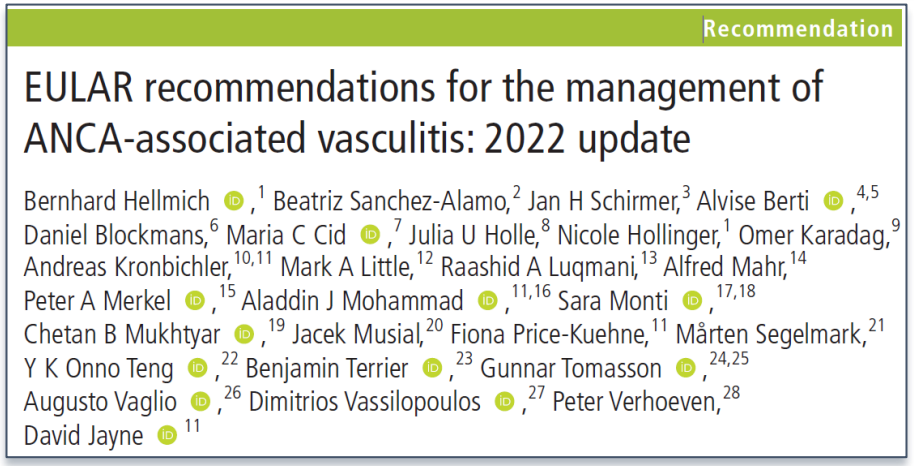
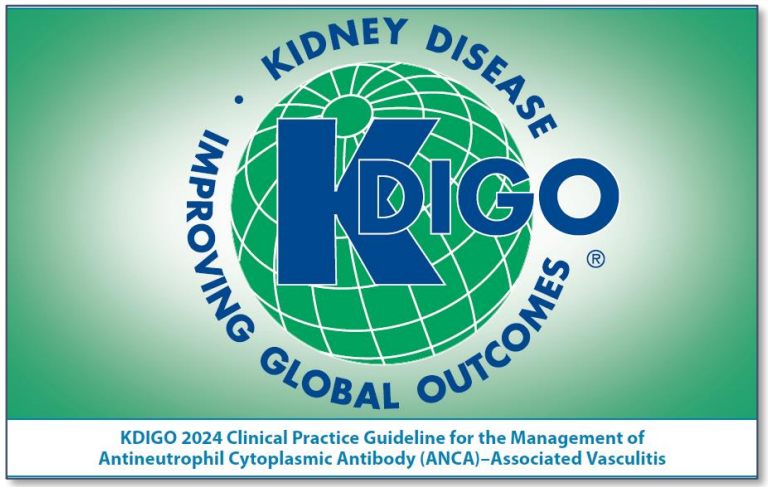
2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Sharon A. Chung,[1] Carol A. Langford,[2] Mehrdad Maz,[3] Andy Abril,[4] Mark Gorelik,[5] Gordon Guyatt,[6] Amy M. Archer,[7] Doyt L. Conn,[8] Kathy A. Full,[9] Peter C. Grayson,[10] Maria F. Ibarra,[11] Lisa F. Imundo,[5] Susan Kim,[1] Peter A. Merkel,[12] Rennie L. Rhee,[12] Philip Seo,[13] John H. Stone,[14] Sangeeta Sule,[15] Robert P. Sundel,[16] Omar I. Vitobaldi,[17] Ann Warner,[18] Kevin Byram,[19] Anisha B. Dua,[7] Nedaa Husainat,[20] Karen E. James,[21] Mohamad A. Kalot,[22] Yih Chang Lin,[23] Jason M. Springer,[3] Marat Turgunbaev,[24] Alexandra Villa-Forte,[2] Amy S. Turner,[24] and Reem A. Mustafa[25]


Recommendation

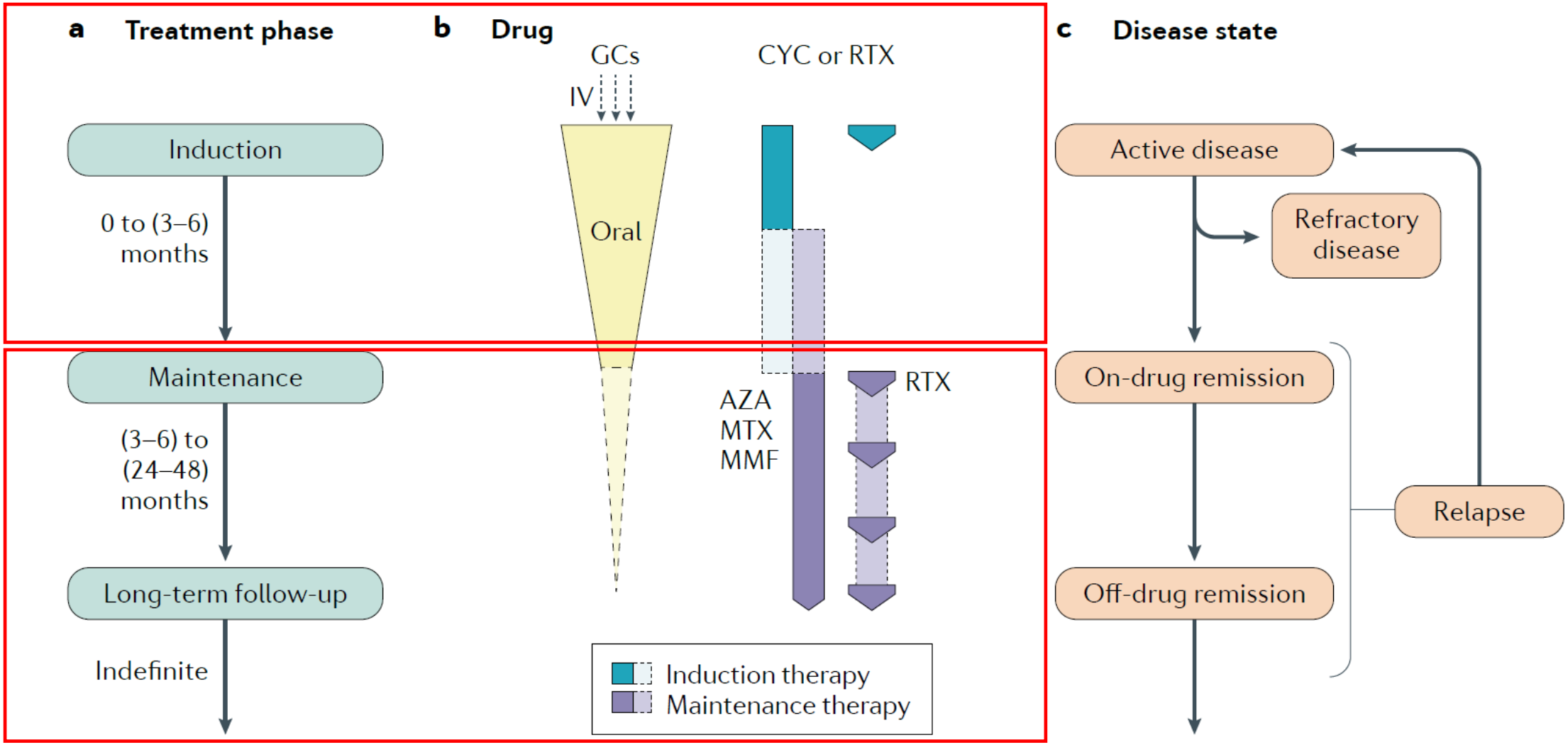
EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

Bernhard Hellmich ,[1] Beatriz Sanchez-Alamo,[2] Jan H Schirmer,[3] Alvise Berti ,[4,5] Daniel Blockmans,[6] Maria C Cid ,[7] Julia U Holle,[8] Nicole Hollinger,[1] Omer Karadag,[9] Andreas Kronbichler,[10,11] Mark A Little,[12] Raashid A Luqmani,[13] Alfred Mahr,[14] Peter A Merkel ,[15] Aladdin J Mohammad ,[11,16] Sara Monti ,[17,18] Chetan B Mukhtyar ,[19] Jacek Musial,[20] Fiona Price-Kuehne,[11] Mårten Segelmark,[21] Y K Onno Teng ,[22] Benjamin Terrier ,[23] Gunnar Tomasson ,[24,25] Augusto Vaglio ,[26] Dimitrios Vassilopoulos ,[27] Peter Verhoeven,[28] David Jayne [11]



KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

Therapy framework in ANCA-associated GN



Kitching et al., Nature Reviews Disease Primers 2020

AAV: Induction therapy options with significant renal involvement
(plus PNL/avacopan)

Rituximab 1g x2
+PNL/AVAC
Trial = **RAVE**

Relapsing disease
PR3-ANCA+

Cyclophosphamide +
PNL/AVAC
IV vs PO = **CYCLOPS**
Cyclophos IV
Reduce: eGFR, age
Wks 0, 2, 4, 7, 10, 13

Cyclophosphamide then
RITUX
+PNL/AVAC
Modifications of RITUVAS
(Units using currently ± rapid GC wean)

Cyclophosphamide PO
daily
Reduce for eGFR
Higher dose
Less relapse

Lower dose iv CYC
500mg x4-6, + PNL

Trial = **CORTAGE**

Weeks 0, 2, 4, 7, (10, 13)

Elderly, frail

MMF po
+PNL
Trial = **MYCYC**
Elderly, frail, MPO-ANCA+, can't get rituximab, concern re infection
* frequent relapse with induction MMF *

1. ANCA-associated vasculitis – Ritux vs Cyclophos

Markedly reduced/rapidly declining GFR (Cr > 350)

- limited data to support rituximab and glucocorticoids.

"Both cyclophosphamide and glucocorticoids, and the combination of rituximab and cyclophosphamide can be considered."

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l])*

*A combination of 2 iv pulses of cyclophosphamide with rituximab can be considered

Should CYC be given at the same time/prior to rituximab in severe disease?

- Relatively common practice – based on retrospective studies and belief
- Trial underway of 6 x 500mg CYC + RTX versus RTX

For

1. The onset of action of rituximab may be slower than cyclophosphamide
2. Rituximab not formally trialled in severe renal failure
3. Front load immunosuppression - use low dose/no glucocorticoids

Against

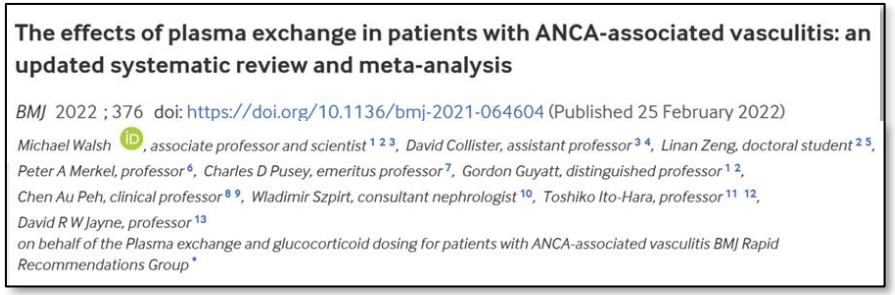
1. Lack of evidence
2. Potential Toxicity

NZ

2. Plasma exchange for severe renal disease in AAV in 2024

Guidelines and interpretation of evidence vary:
Suggest:

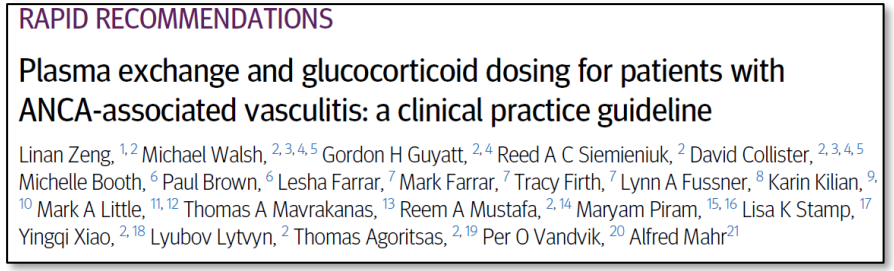
- Use with double positive anti-GBM/ANCA
- Little good evidence for routine use in alveolar haemorrhage
- Consider if high risk ESKD and acceptable risk of infection/other complications
- Consider risk/benefits
  - It is a procedure – factor in access to PLEX and the experience of the operators
- Aim to involve the patient in the decision



The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis

BMJ 2022 ; 376 doi: https://doi.org/10.1136/bmj-2021-064604 (Published 25 February 2022)

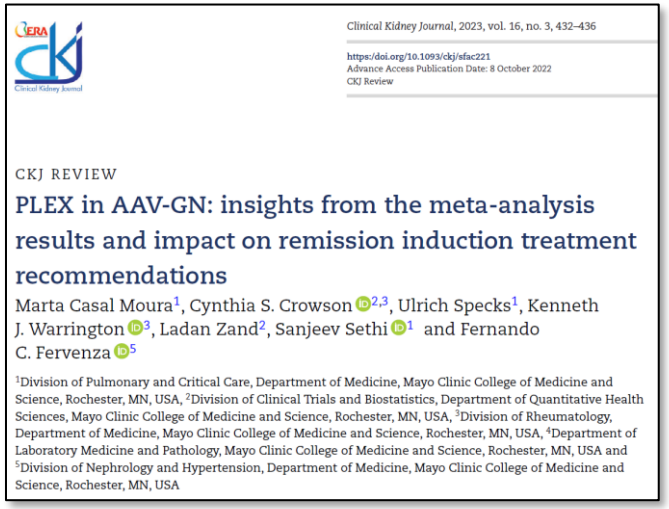
Michael Walsh, associate professor and scientist [1 2 3], David Collister, assistant professor [3 4], Linan Zeng, doctoral student [2 5], Peter A Merkel, professor [6], Charles D Pusey, emeritus professor [7], Gordon Guyatt, distinguished professor [1 2], Chen Au Peh, clinical professor [8 9], Wladimir Szpirt, consultant nephrologist [10], Toshiko Ito-Hara, professor [11 12], David R W Jayne, professor [13]
*on behalf of the Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis BMJ Rapid Recommendations Group **



RAPID RECOMMENDATIONS

Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis: a clinical practice guideline

Linan Zeng, [1,2] Michael Walsh, [2,3,4,5] Gordon H Guyatt, [2,4] Reed A C Siemieniuk, [2] David Collister, [2,3,4,5] Michelle Booth, [6] Paul Brown, [6] Lesha Farrar, [7] Mark Farrar, [7] Tracy Firth, [7] Lynn A Fussner, [8] Karin Kilian, [9,10] Mark A Little, [11,12] Thomas A Mavrakanas, [13] Reem A Mustafa, [2,14] Maryam Piram, [15,16] Lisa K Stamp, [17] Yingqi Xiao, [2,18] Lyubov Lytvyn, [2] Thomas Agoritsas, [2,19] Per O Vandvik, [20] Alfred Mahr[21]



Clinical Kidney Journal, 2023, vol. 16, no. 3, 432–436

https://doi.org/10.1093/ckj/sfac221
Advance Access Publication Date: 8 October 2022
CKJ Review

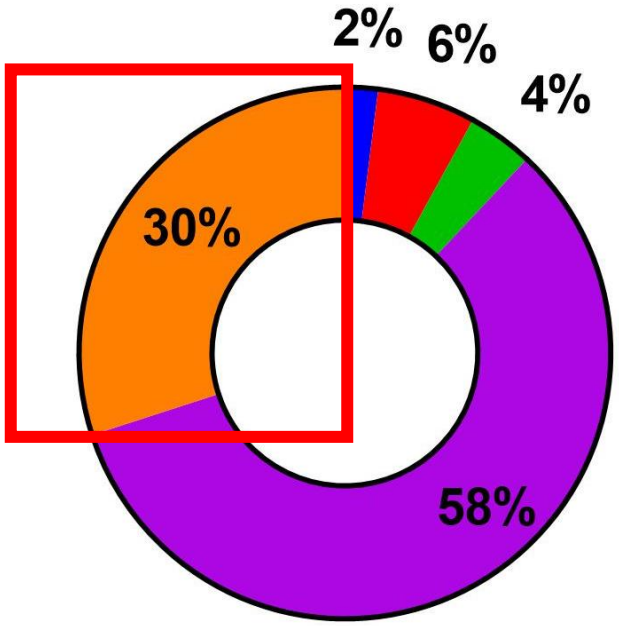
CKJ REVIEW

PLEX in AAV-GN: insights from the meta-analysis results and impact on remission induction treatment recommendations

Marta Casal Moura[1], Cynthia S. Crowson [2,3], Ulrich Specks[1], Kenneth J. Warrington [3], Ladan Zand[2], Sanjeev Sethi [1] and Fernando C. Fervenza [5]

[1]Division of Pulmonary and Critical Care, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA, [2]Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic College of Medicine and Science, Rochester, MN, USA, [3]Division of Rheumatology, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA, [4]Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA and [5]Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA

3. Glucocorticoid dose: PEXIVAS (2020)
~ halving of GC dose



A No prednisolone

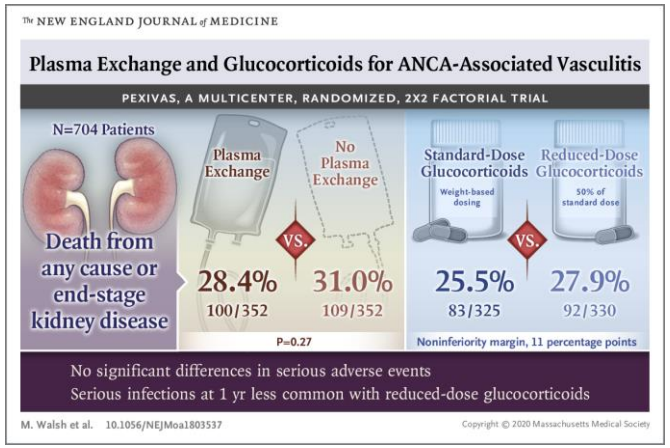
B No set plan and based on assessment of response

C Very low dose prednisolone and rapid wean

D Reduced dose predisolone regimen in PEXIVAS trial

E Standard dose prednisolone regimen in PEXIVAS trial

**** 30%****



ANZ Vasculitis Survey:
Acute severe ANCA-associated GN

Chua J et al, Internal Med J 2024

MPO-AAV without critical renal injury, rituximab + low dose GCs?

JAMA | Original Investigation

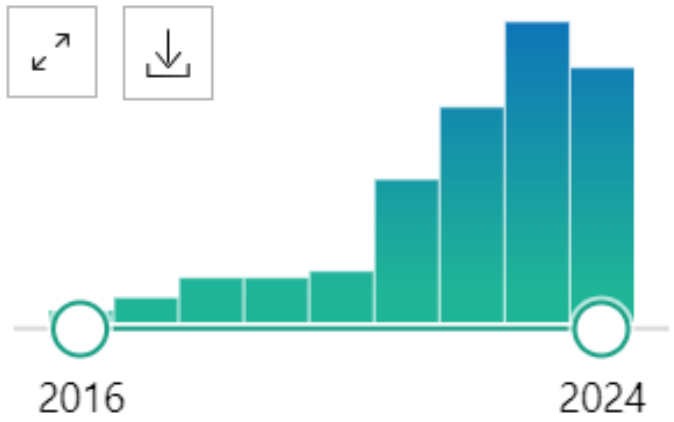
Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis
A Randomized Clinical Trial

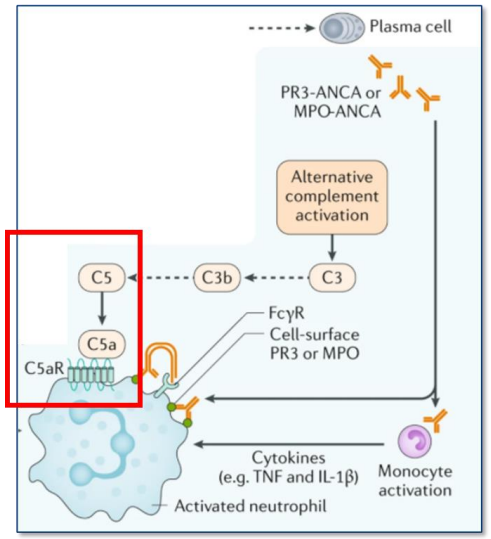
Shunsuke Furuta, MD, PhD; Daiki Nakagomi, MD, PhD; Yoshihisa Kobayashi, MD, PhD; Masaki Hiraguri, MD; Takao Sugiyama, MD, PhD; Koichi Amano, MD, PhD; Takeshi Umibe, MD, PhD; Hajime Kono, MD, PhD; Kazuhiro Kurasawa, MD, PhD; Yasuhiko Kita, MD, PhD; Ryutaro Matsumura, MD, PhD; Yuko Kaneko, MD, PhD; Keita Ninagawa, MD; Keiju Hiromura, MD, PhD; Shin-ichiro Kagami, MD, PhD; Yosuke Inaba, PhD; Hideki Hanaoka, MD, PhD; Kei Ikeda, MD, PhD; Hiroshi Nakajima, MD, PhD; for the LoVAS Collaborators

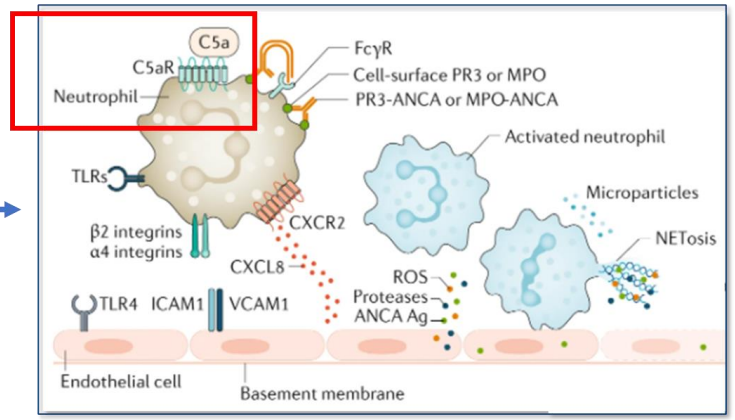
4. Avacopan: still early days –heavy reliance on ADVOCATE for evidence

"Avacopan AND [ANCA-associated] Vasculitis" (PubMed 24 August 2024)

145 Publications



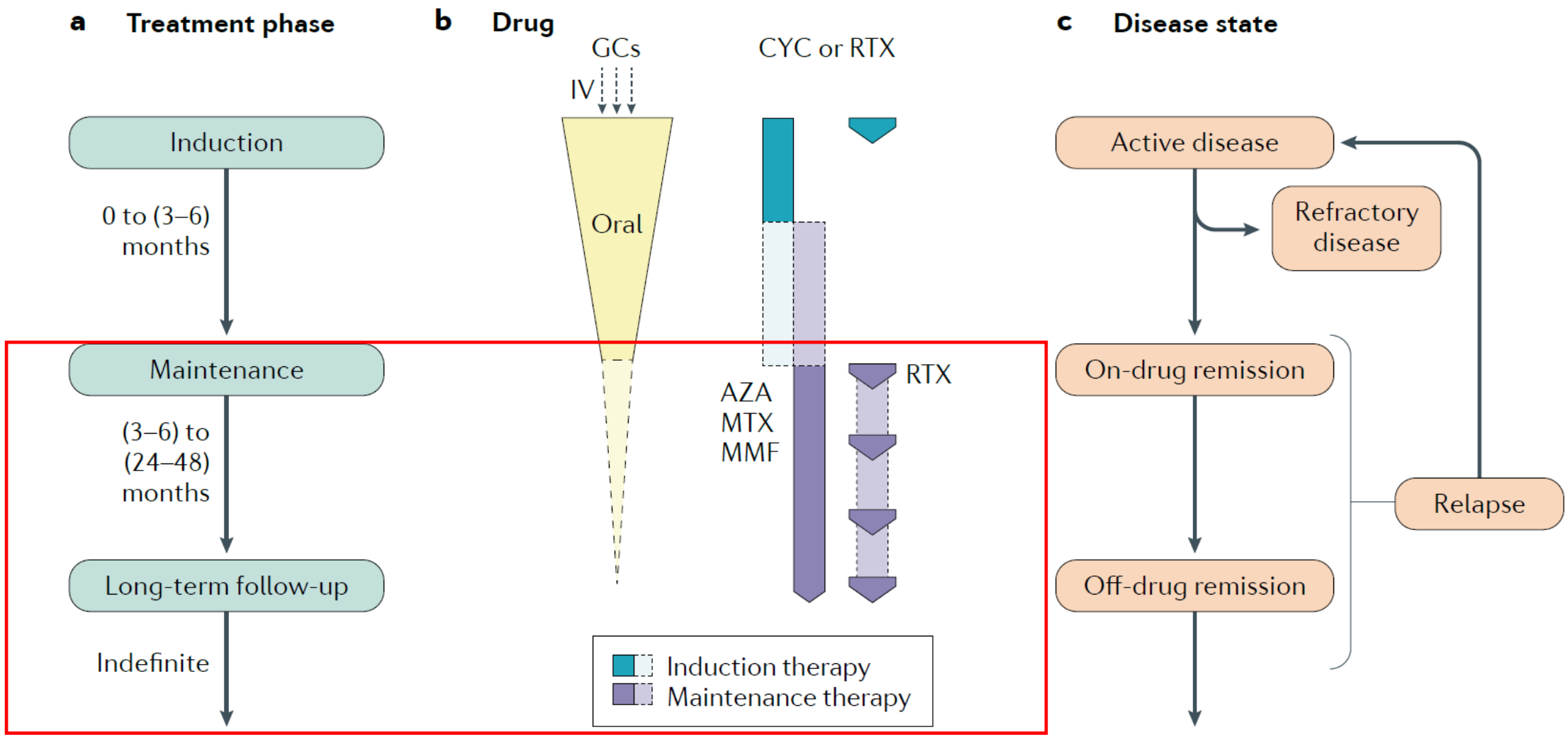




- **92** reviews/comments/editorials/surveys/letters/corrections
- **4** Clinical trials **13** publications
  - One Phase 3: ADVOCATE: Protocol, Trial, 7 Subanalyses
- **2** Pharmokinetic studies
- **9** Case series
- **16** Case reports
- **3** Cost/economic analyses

NZ

Maintenance therapy



Kitching et al., Nature Reviews Disease Primers 2020

Maintenance options in AAV with significant renal involvement

Rituximab > Azathioprine ≥ MTX > MMF Duration unclear: 2-4+ years, impacted by PR3- vs MPO-AAV, previous relapse, patient-specific factors

Wean PNL over time to <5mg/stop

TAPIR: generally safe to stop if Ritux

Rituximab

First line
(watch for hypogamma)

Maintenance Ritux
(4-)6 monthly for 2+ years
OR can
dose on B cell/ANCA return
(measure 3 monthly)

No IS following rituximab induction (RAVE) only in particular patient specific circumstances

Azathioprine (+PNL)

1.5-2 mg/kg/d

(Low IgG HepBsAg+)

Continue AZA 2-4+ yr

1.5-2mg/kg ~18-24 months
Then slow taper

MMF + PNL

AZA Intolerant/ Can't get RITUX/

Induction with MMF

Continue MMF 2-4+ yr (as per AZA)

Other:
MTX + PNL
Leflunomide + PNL

Good renal function (MTX) Intolerant of AZA Lef (30mg dose)

Continue 2-4+ yr (as per AZA)

NZ

When to stop maintenance therapy?
Ongoing morbidity and long term damage: patient preference: disease vs drug

Continuing treatment

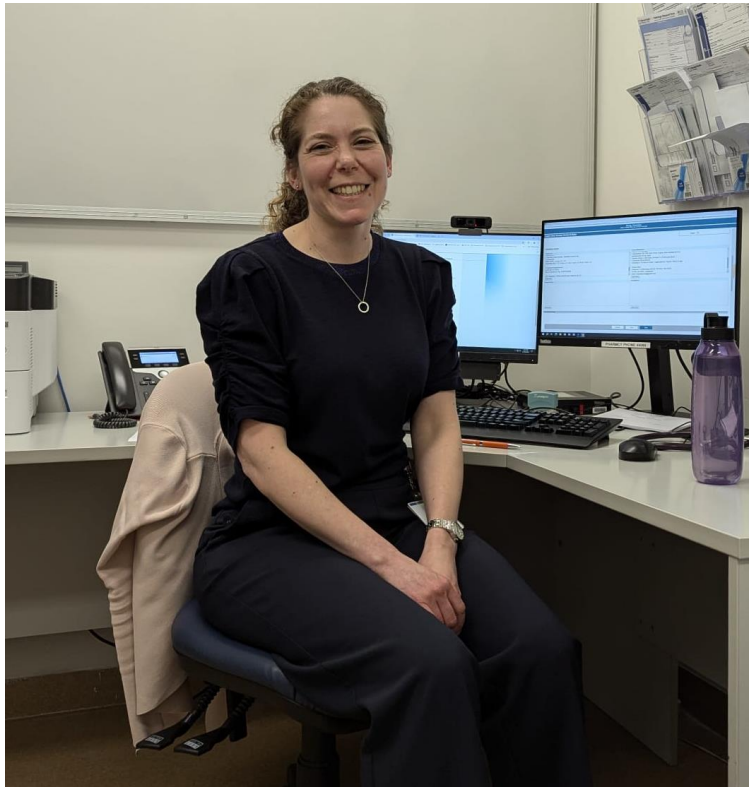
- Pt preference to avoid relapse
- PR3-AAV
- Previous relapse
- Positive ANCA (esp. PR3-ANCA)
- Significant disease damage already
- Little treatment associated damage
- Tolerating treatment well
  - No side effects, infection, other comorbidities
- SE of high dose re-induction if relapse

Stopping/reducing treatment

- Pt preference to stop medication
- MPO-AAV
- No previous relapse
- Negative ANCA
- Little organ/tissue damage
- Significant treatment associated damage
- Poor tolerance of treatment
  - Significant infections, side effects, other comorbidities
- Well placed to avoid major SE if re-induction

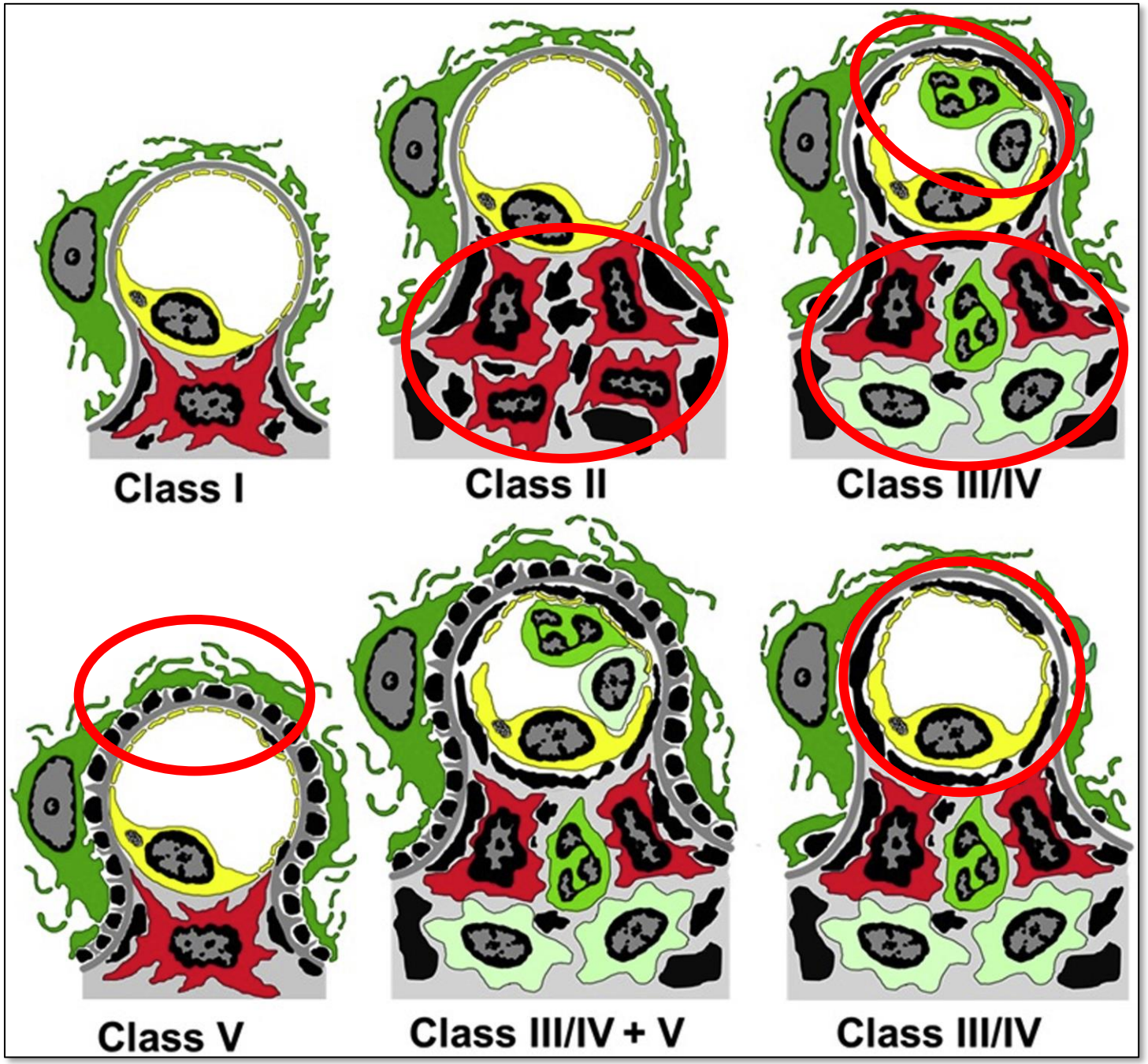
Lupus Nephritis

Prof Brad Rovin, Ohio State
Co-chair, KDIGO LN working group



Dr Joanna Kent, Lead Nephrologist
Monash Lupus Clinic

ISN/RPS Lupus Nephritis Classes



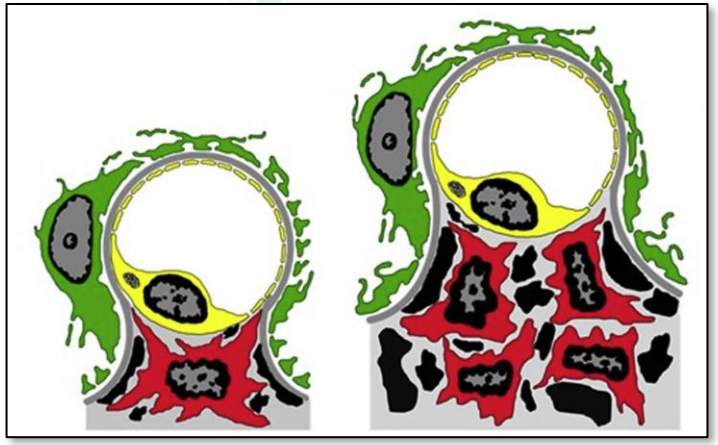
Bajema IM et al, Kidney Int 2018

Components of the activity index	Score	Calculating the activity score Extent of lesion	Points
• Endocapillary hypercellularity	0–3	Not present	0
• Neutrophils and/or karyorrhexis	0–3	Present in <25%	1
• Fibrinoid necrosis	(0–3) × 2	Present in 25%–50%	2
• Hyaline deposits (wire loop and/or hyaline thrombi)	0–3	Present in >50%	3
• Cellular/fibrocellular crescents	(0–3) × 2		
• Interstitial inflammation (interstitial leukocytes)	0–3		
	Total: 0–24		

Items included into the NIH chronicity score	Score	Calculating the chronicity score Extent of lesion	Points
• Total glomerulosclerosis (global + segmental)	0–3	Present in <10%	0
• Fibrous crescents	0–3	Present in 10%–25%	1
• Interstitial fibrosis	0–3	Present in 25%–50%	2
• Tubular atrophy	0–3	Present in >50%	3
	Total: 0–12		

Other histologic findings not included in the activity or chronicity score
• Foot process effacement (lupus podocytopathy) • Collapsing lupus glomerulopathy • Vascular lesions (arteriosclerosis, non-inflammatory vascular immune complex deposits, thrombotic microangiopathy, non-inflammatory necrotizing vasculitis, true renal vasculitis)

Class I or II LN



Kidney biopsy showing Class I/II lupus nephritis

- Low-level proteinuria
  - Immunosuppressive treatment guided by extrarenal manifestations of systemic lupus erythematosus
- Nephrotic syndrome
  - Evaluate for lupus podocytopathy (electron microscopy would be useful)
  - Treat as minimal change disease
  - Consider maintenance combination therapy with low-dose glucocorticoid and another immunosuppressive agent

Class III or Class IV LN: Initial therapy

Biopsy with LN Class III/IV ± V

Plus TMA?

Activity Chronicity

Active

Glucocorticoids

All Level IB evidence

- MMF
- Cyclophosphamide
- CNI + MMF
- Belimumab + MMF/low dose CYC

Chronic

If Class V: Manage as V

No Class V: Supportive

Class III or Class IV: glucocorticoids

	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Lupus Nephritis – Class III or Class IV LN: Initial therapy

MMF (standard of care at Monash) 2-3g per day. Use especially if

- High risk of infertility
- Moderate/high prior cyclophosphamide exposure.

CNI *tacrolimus* (cyclosporine, [voclosporin]) **and reduced dose MMF:**

- Good kidney function (eGFR >45) + nephrotic-range proteinuria ?podocyte injury
- Can't tolerate 2-3g MMF + can't/won't use cyclophosphamide
  - MMF 1g/day
  - Tacrolimus to level ~ 4-6 ug/L

Class III or Class IV: cyclophosphamide

	High-dose intravenous cyclophosphamide (NIH regimen)	Low-dose intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m^2 monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months
Comments	Efficacy data included patients of different races/ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of African or Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

Class III or Class IV LN: Initial therapy

Belimumab + glucocorticoids + either MMF/reduced-dose cyclophosphamide

- Repeated kidney flares/high-risk for progression
- Belimumab 10mg/kg 2 weekly x 3, then four weekly

Rituximab

- Persistent disease activity/inadequate response to initial standard-of-care therapy.

Azathioprine or leflunomide with glucocorticoids, *in lieu* of the recommended initial drugs

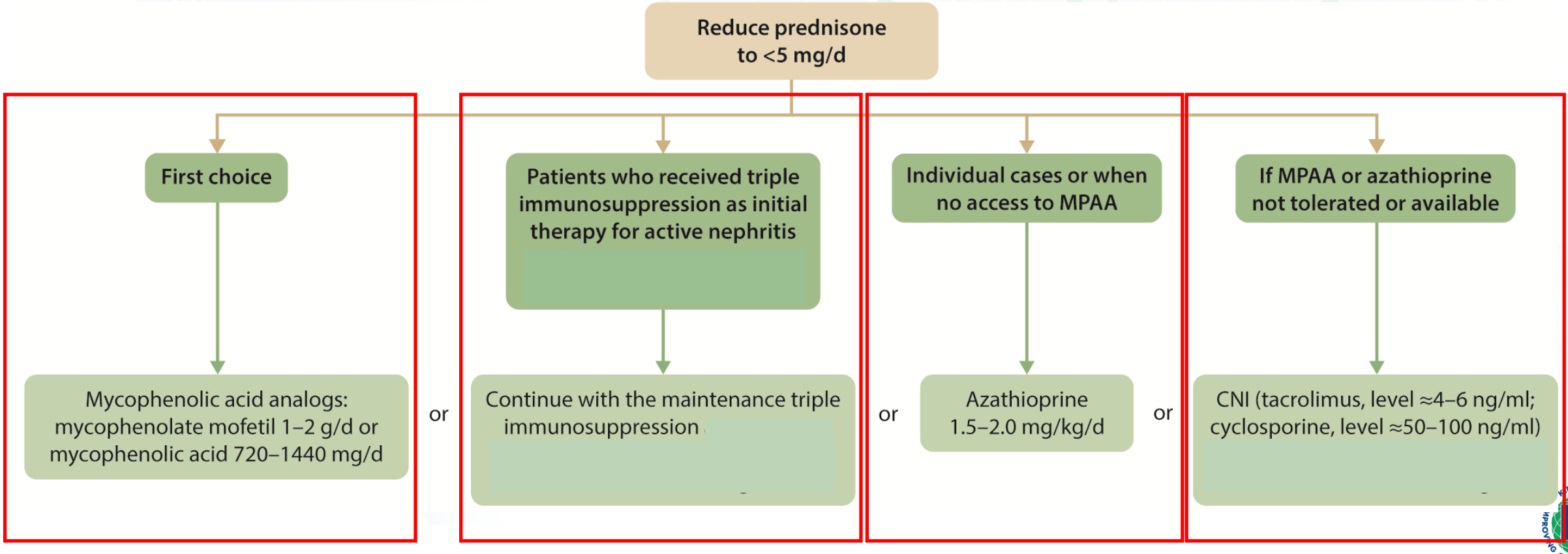
- Patient intolerance
- May be less effective and/or more toxic

Newer biologic, non-biologics and cell therapies

- Under development and may offer future options

Class III or Class IV LN: Maintenance therapy

Total **duration** of immunosuppression for LN III or IV: ≥36 months
Mycophenolate (*1B*): early maintenance 1.5-2g, reduce to ~1 g/d over time
Glucocorticoids: lowest possible dose, consider stop >12 months in remission



Class V LN *without* evidence of (active) Class III/IV

Kidney biopsy showing Class V lupus nephritis

Low-level proteinuria

Nephrotic-range proteinuria

Monitor the level of proteinuria and prevent or treat complications (e.g., thrombosis, dyslipidemia, edema)

1 Renin-angiotensin system blockade and blood pressure control
2 Immunosuppressive treatment guided by extrarenal manifestations of systemic lupus erythematosus
3 Hydroxychloroquine

1 Renin-angiotensin system blockade and blood pressure control
2 Combined immunosuppressive treatment with glucocorticoid and one other agent (e.g., mycophenolic acid analogs, cyclophosphamide, calcineurin inhibitor, rituximab, azathioprine). Insufficient data for recommendation of glucocorticoid regimen, but moderate or reduced dose preferred.
3 Hydroxychloroquine

If proteinuria worsens and/or complications of proteinuria develop (e.g., thrombosis, dyslipidemia, edema), consider immunosuppressive therapy

Unsatisfactory Treatment Response

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative recommended treatment regimen when there is persistent active disease
5	Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible

Lupus Nephritis and Pregnancy

Acknowledge and discuss pregnancy as an option for women – be supportive in concept, and emphasize planning

Avoid/counsel against pregnancy

- In active LN
- With potentially teratogenic drugs (MMF/Cyclophosphamide)
- Consider risks of significant ongoing proteinuria/CKD

Pregnancy planning

- Glucocorticoids, hydroxychloroquine, azathioprine, tacrolimus, cyclosporine considered safe/usable
- ≥6 months after LN becomes inactive
- >3 months off MMF (Aza conversion)
- Continue hydroxychloroquine
- Start low-dose aspirin before 16 weeks of gestation.

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