Granulomatosis with polyangiitis

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Diagnosis and management of ANCA-associated vasculitis

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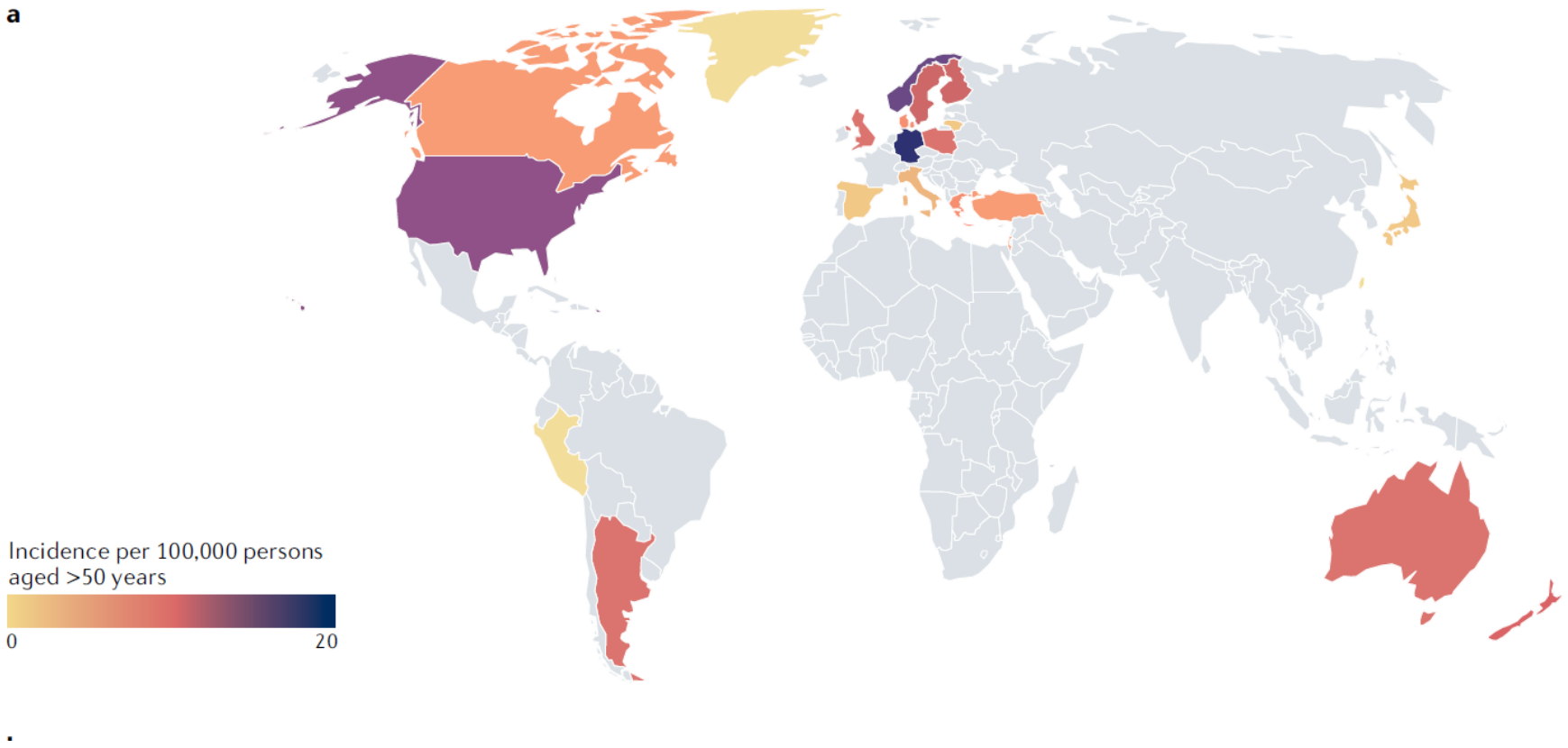
Lancet 2024; 403: 683–98

Introduction

- Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibody–associated vasculitis.
- Characterized by a necrotizing vasculitis that can involve almost any organ.
- The diseases commonly affect the kidneys, lungs, upper respiratory tract, skin, eyes, and peripheral nerves.
- *Lancet* 2024; 403: 683–98

Epidemiology



Nature,January 2022 | volume 18

- A global study reported that MPO-ANCA was much more common in Japanese, Chinese, and Southern European individuals than in Northern European individuals.

- In the same study, ophthalmological and ear, nose and throat involvement was less common in Japanese and Chinese patients with AAV than in Northern European patients with AAV.

- In a multi-ethnic series from Chapel Hill in the USA, **GPA was less common in African American** individuals than in those with European ancestry

Nature,January 2021,volume 18

Pathogenesis of Antineutrophil Cytoplasmic Autoantibody–Associated Small-Vessel Vasculitis

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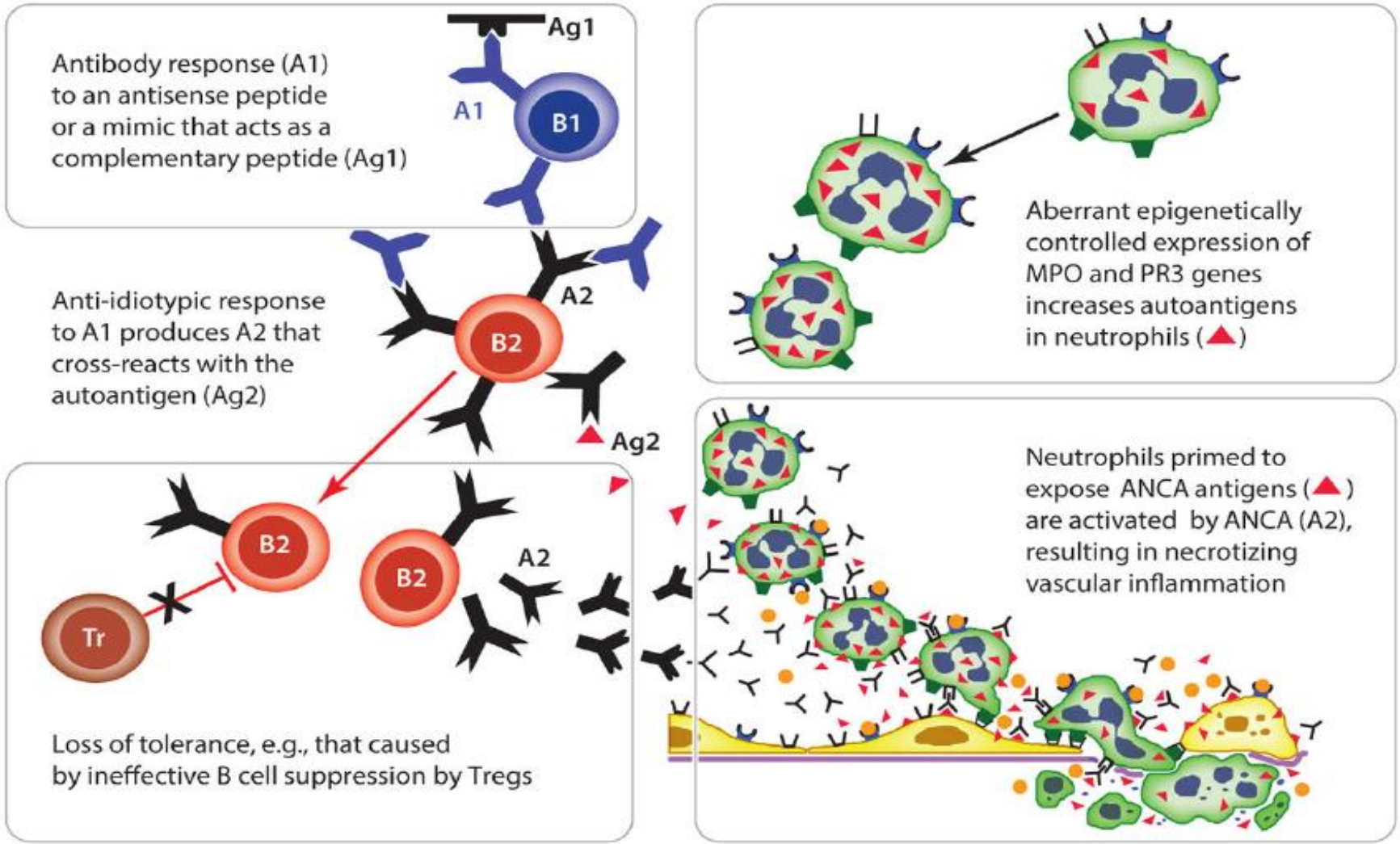
Abstract

- Clinical, in vitro, and experimental animal observations indicate that antineutrophil cytoplasmic autoantibodies (ANCA) are pathogenic.
- The genesis of **the ANCA autoimmune response** is **a multifactorial process** that includes:
- **genetic predisposition**,(HLADPB1,A1AT/SERPINA,PRTN3, CD226 and FCGR3B)
- **environmental adjuvant factors**,
- **an initiating antigen**,
- **failure of T-cell regulation**

- . Annu Rev Pathol. 2013 January 24; 8: 139–160


Antibody response (A1)
to an antisense peptide
or a mimic that acts as a
complementary peptide (Ag1)
Ag1
A1
B1
Anti-idiotypic response
to A1 produces A2 that
cross-reacts with the
autoantigen (Ag2)
A2
B2
Ag2
B2
B2
A2
Tr
Loss of tolerance, e.g., that caused
by ineffective B cell suppression by Tregs
Aberrant epigenetically
controlled expression of
MPO and PR3 genes
increases autoantigens
in neutrophils (▲)
Neutrophils primed to
expose ANCA antigens (▲)
are activated by ANCA (A2),
resulting in necrotizing
vascular inflammation

- Current clinical analytical methods have revealed that **at least 80% to 90%** of **MPA, GPA, and renal-limited** pauci-immune NCGN patients **have ANCA**, as do approximately **40% of EGPA** patients.

- However, **more than 90% of** patients with **EGPA who have NCGN have ANCA .**

- In **North America and Europe, PR3-ANCA cases are more frequent** than MPO-ANCA **in GPA patients**, whereas MPO-ANCA are more frequent than PR3-ANCA in MPA, EGPA, and renal-limited pauci-immune NCGN patients

- In **Asia, MPO-ANCA is much more frequent** relative to PR3-ANCA than in Europe and North America.

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Pathology of GPA

- AAV is a necrotizing small-vessel vasculitis (SVV) that affects predominantly **capillaries, venules, arterioles** and small arteries, and (less often) medium arteries and veins .
- In addition to AAV, which typically has a **paucity of immunoglobulin** deposited in vessel walls.
- The **SVV category** also **includes** various vasculitides that have conspicuous vessel wall immunoglobulin and complement deposits, such as **Henoch–Schönlein purpura vasculitis** (IgA vasculitis), **cryoglobulinemic vasculitis**, and **anti–glomerular basem**ent membrane disease (anti-GBM disease

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- **ANCA** binds to antigens in the primary granules of **neutrophils** and the peroxidase-positive lysosomes of **monocytes**.

- (**MPO**) and (**PR3)** are two major antigens recognized by ANCA in patients with vasculitis and glomerulonephritis.

- Lysosomal-associated membrane protein 2 **(LAMP2**) has also been proposed as a major target for ANCA.

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- The vasculitis of **GPA can be pathologically** identical to that of **MPA**.

- GPA g**ranulomatous** inflammation is most common in the **upper o**r **lower respiratory** tract but can occur anywhere, including the orbit, **skin,** and **meninges**.

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- The **acute lesions** have **intense neutrophilic infiltration** that resembles abscess formation, rather than a monocyte- and T cell–rich cell-mediated immune response.
- The **primary granulomatous** feature in the acute phase is the presence of **multinucleated giant cells.**
- Acute lesions may have **focal accumulations of fibrinoid material**, indicating substantial **vascular exudation or vascular disruption**, even though necrotic vessels are not identifiable in the lesions.

- As the **lesions progress**, they develop more classic features of **granulomatous inflammation**; there are **palisading macrophages** and **giant cells at the margins of zones of necr**osis that are composed of amorphous necrotic debris .
- At low magnification, **larger zones of necrosis have an irregular** outline that is referred to as **geographic necrosis.**

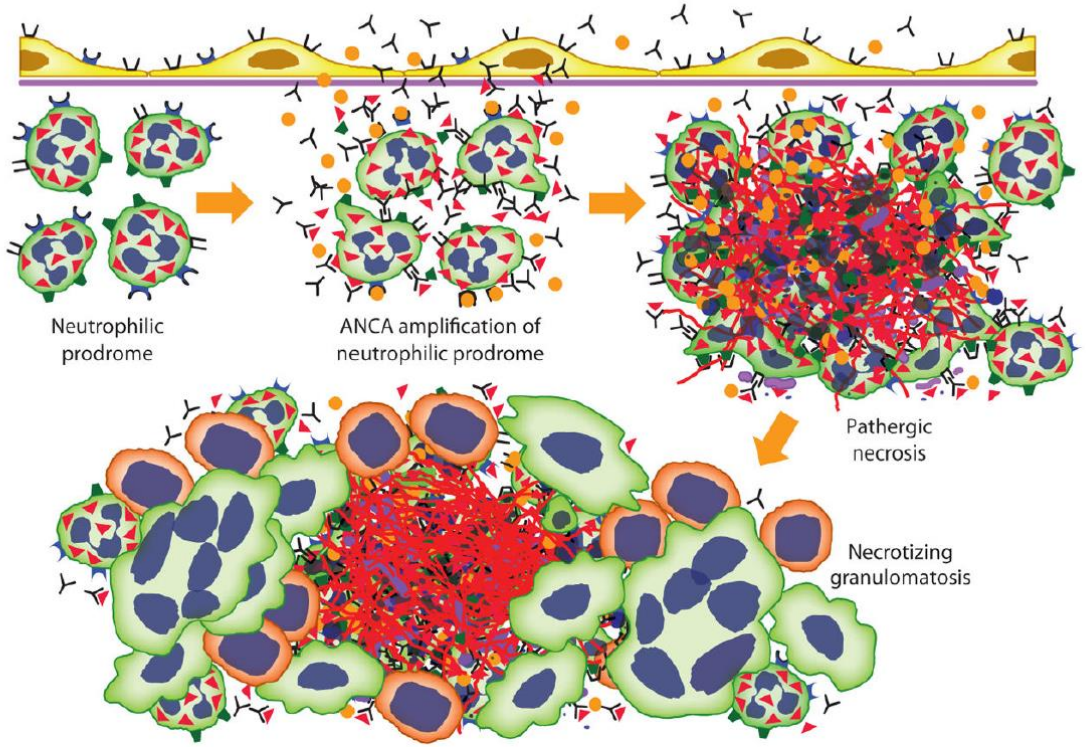

Figure 7.
Putative events in the pathogenesis of extravascular granulomatosis. (*Upper left*) Extravascular neutrophils are activated to produce (*upper middle*) intense localized acute inflammation, which causes (*upper right*) tissue necrosis and fibrin formation. The acute injury elicits a mononuclear leukocyte response, including (*bottom*) the influx of monocytes that transform into macrophages and multinucleated giant cells.

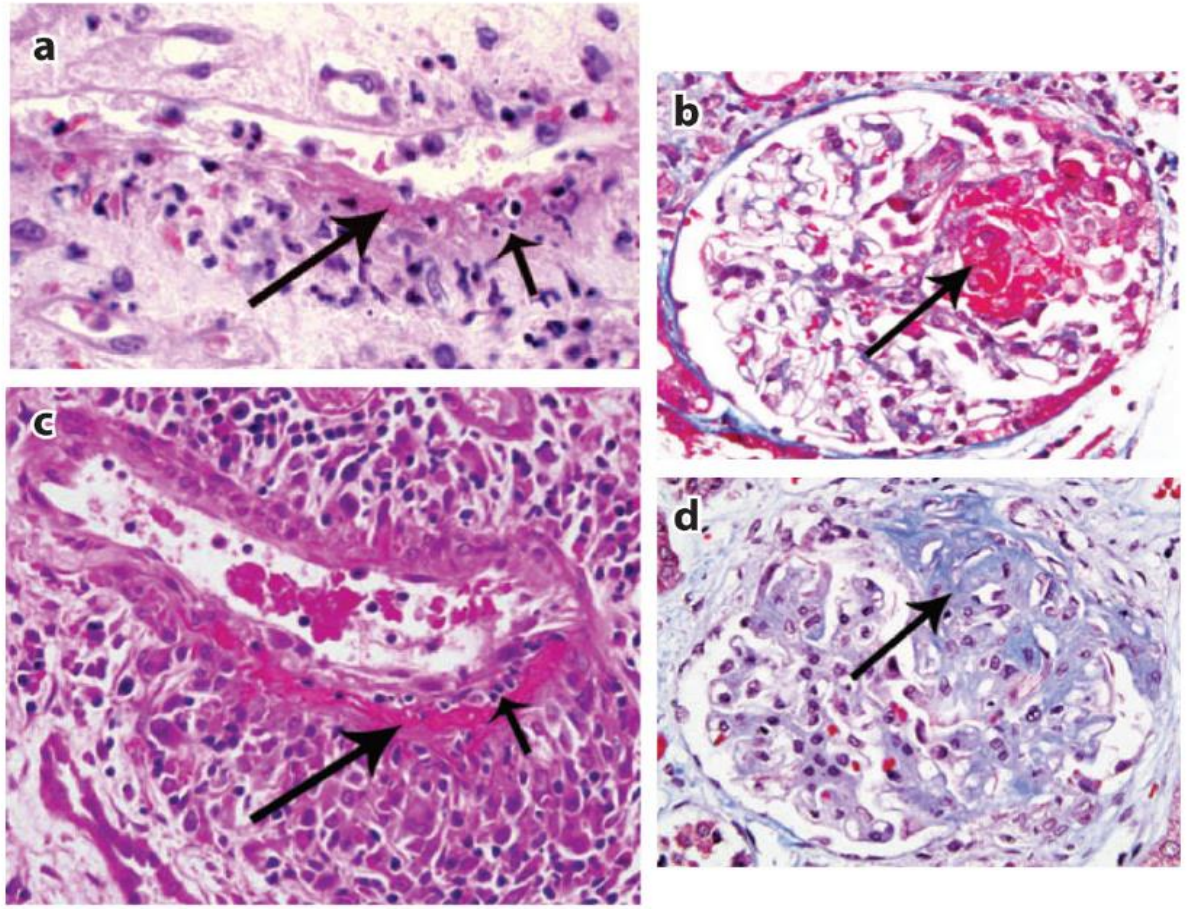

Figure 1.
Segmental acute necrotizing ANCA-associated vasculitis lesions with (*a–c*) fibrinoid necrosis (hematoxylin and eosin stain) (*large arrow*) and (*a,c*) leukocytoclasia (*small arrow*). (*a,b*) The inflammatory infiltrate includes a mixture of neutrophils and mononuclear leukocytes. (*c,d*) A Masson trichrome stain is useful in distinguishing between (*b*) acute segmental fibrinoid necrosis and (*d*) chronic segmental sclerosis.

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CLINICAL EVIDENCE FOR ANCA PATHOGENICITY

- The **high frequency of ANCA** in patients with very distinctive **pathologic lesions** suggests the possibility, but does not prove, that the production of ANCA is involved in the pathogenesis of these lesions.

- More incriminating is the **correlation of ANCA titers** with response to treatment and **with recurrence of disease** , but this correlation is not uniform.
- The efficacy of **anti–B cell therapy** and of **plasma exchange** in treating ANCA-associated vasculitis is consistent with an **important role for antibodies in pathogenesis.**

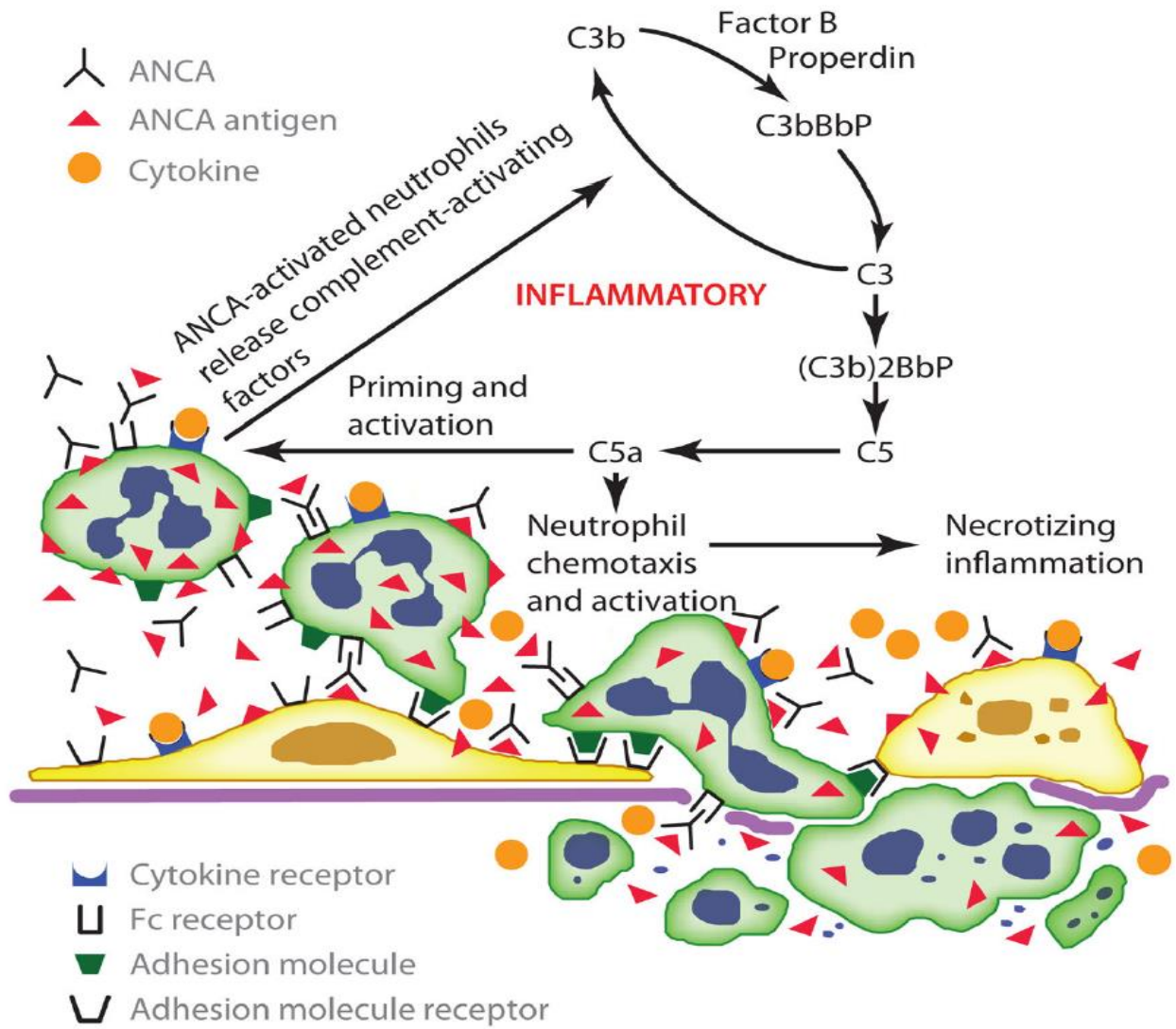
- Specific drugs induce ANCA formation; these include **propylthiouracil**, **allopurinol**, **D-penicillamine**, **hydralazine**, and **levamisole** (which may be a contaminant of cocaine).
- Patients with drug-induced ANCA may develop lesions that are indistinguishable from those of MPA, GPA, or EGPA.

IN VITRO EVIDENCE FOR ANCA PATHOGENICITY

- Activation of neutrophils by ANCA requires the availability of low numbers of **antigens at the neutrophil surface** to interact with antibodies. Some antigens, especially PR3, may be present constitutively on normal neutrophils.

- **Neutrophils** must be **stimulated (primed) by inflammatory stimuli** (e.g., cytokines) to release ANCA antigens at the surface or in the nearby microenvironment.

- Markedly **enhanced activation** of neutrophils by **ANCA IgG** after priming with **low doses of (TNF-α),** which induces **surface release** and **binding of MPO and PR3** from neutrophils.

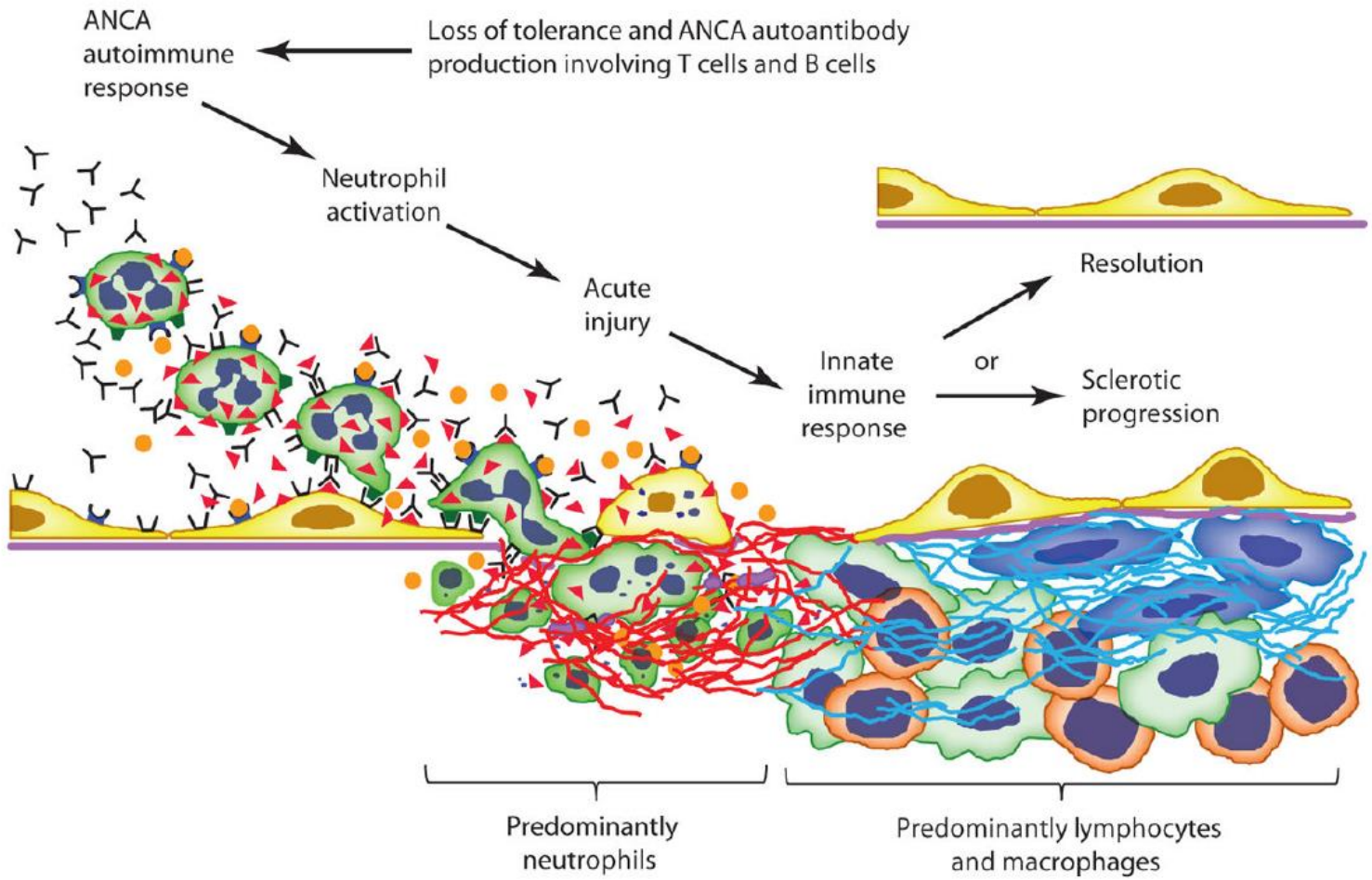

ANCA
ANCA antigen
Cytokine
C3b
Factor B
Properdin
C3bBbP
C3
INFLAMMATORY
(C3b)2BbP
C5
C5a
ANCA-activated neutrophils release complement-activating factors
Priming and activation
Neutrophil chemotaxis and activation
Necrotizing inflammation
Cytokine receptor
Fc receptor
Adhesion molecule
Adhesion molecule receptor

IN VITRO EVIDENCE FOR ANCA PATHOGENICITY

- **Incubation of normal human neutrophils** with **MPO ANCA immunoglobulin G (IgG**) or **PR3-ANCA IgG** results in activation, causing a respiratory burst that generates toxic **oxygen radicals** and **degranulation** that releases **numerous destructive enzymes.**

- **ANCA IgG from AAV patients** with **active disease** cause more in vitro activation than do ANCA from patients in remission .
- This finding suggests that there may be **certain ANCA antibody classes** or **epitope specificities** that are more pathogenic than others.

- Endothelial injury by ANCA-activated neutrophils has been demonstrated in **multiple in vitro systems**.
- **Incubation of neutrophils and ANCA IgG** with **endothelial monolayers** causes the **death of endothelial cells**.
- This process is **facilitated by cytokine priming of both neutrophils** and **endothelial cells**.
- **Flow-based adhesion assays** have demonstrated that **ANCA can stimulate** neutrophils to **adhere to and penetrate** **through endothelial m**onolayers, mediated by **integrins and chemokines**, which simulates events that occur in AAV.


ANCA
autoimmune
response
Loss of tolerance and ANCA autoantibody
production involving T cells and B cells
Neutrophil
activation
Acute
injury
Innate
immune
response
or
Resolution
Sclerotic
progression
Predominantly
neutrophils
Predominantly lymphocytes
and macrophages

Diagnosis

- The diagnosis of ANCA-associated vasculitis relies on information from
- **Clinical evaluations**
- **Serological findings**
- **Radiological data**
- **Pathology results**

- **Delays in diagnosis** are reported by approximately **60%** of patients with ANCA-associated vasculitis.
- The **median time between symptom onset** and final diagnosis is **6 months.**

- Patients with **ear, nose, and throat-limited** disease are often **ANCA negative** and have **radiological findings of low specificity**.

- Moreover, **biopsies** from the upper respiratory tract often have low diagnostic yield, revealing **non-specific inflammation** rather than granulomatous disease, and showing **vasculitis in only a third** of biopsies.
- Characteristic histological lesions must be **differentiated** from **non-specific** lesions, and **vasculitis mimics** need to be excluded for an accurate diagnosis.

Review

Granulomatosis with polyangiitis (Wegener): Clinical aspects and treatment

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Autoimmunity Reviews 13 (2014) 1121–1125

Clinical Manifestations

- Constitutional signs (fever, asthenia,weight loss) are frequent (50%) but non-specific.

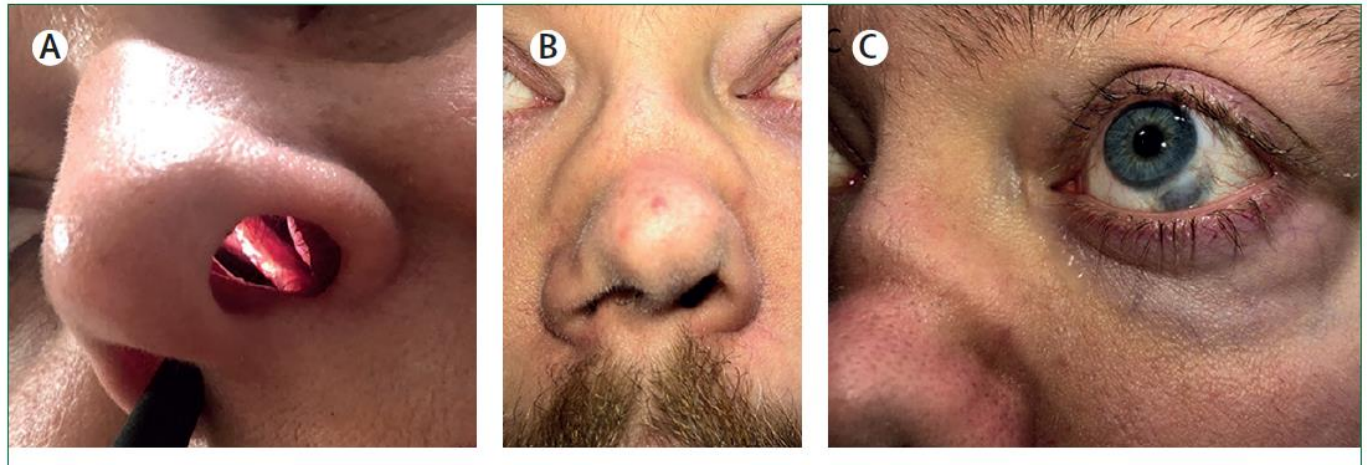
	Granulomatosis with polyangiitis*	Microscopic polyangiitis*	PR3-ANCA-associated vasculitis†	MPO-ANCA-associated vasculitis‡
General	77·7%	85·8%	81%	91·7%
Body temperature ≥38°C	30·7%	35·4%	44·3% (≥38·5°C)	..
Fatigue	56·4%	68·0%	-	..
Weight loss ≥2 kg	34·7%	43·1%	46·7% (>3 kg)	..
Arthralgia	54·5%	31·7%	56·4%	..
Myalgia	22·1%	24·3%	26·2%	..
Cutaneous	34·7%	29·5%	33·9%	16·7%
Petechiae or purpura	16·8%	9·5%	17·9%	..
Mucous membranes or eyes	38·3%	12·9%	28·2%	10·4%
Scleritis or episcleritis	13·5%	0·6%	4·9% (scleritis) and 10·4% (episcleritis)	..
Ear, nose, and throat	82·3%	25·8%	81·0%	2·1%
Respiratory	63·1%	62·8%	68·1%	50·0%
Haemoptysis or diffuse alveolar haemorrhage	21·1%	19·4%	17·8%	22·2%
Cardiovascular	10·7%	15·1%	15·9%	6·3%
Abdominal	18·7%	22·2%	11·2%	3·5%
Renal	58·6%	82·2%	57·7%	79·2%
Neurological	31·2%	36·6%	30·0%	38·9%
Neuropathy	11·9%	25·8%	20·7%	20·8%
Mononeuritis multiplex	4·9%	8·6%	..	..
Sensory neuropathy	11·1%	21·2%	..	..

ANCA=antineutrophil cytoplasmic antibody. MPO=myeloperoxidase. PR3=proteinase 3. *Data are from 674 patients with granulomatosis with polyangiitis and 325 patients with microscopic polyangiitis as reported in the Diagnostic and Classification Criteria in Vasculitis (DCVAS) study,[20] an international study involving 32 countries. †Data are from 546 patients with PR3-ANCA-associated vasculitis reported from the French Vasculitis Study Group (FVSG).[21] ‡Data are from 144 patients with MPO-ANCA vasculitis from a single centre in Germany.[22] Data also contain six patients with PR3-ANCA-associated vasculitis.

Table 2: **Disease manifestations in granulomatosis with polyangiitis, microscopic polyangiitis, PR3-ANCA-associated vasculitis, and MPO-ANCA-associated vasculitis**

- Ear, nose and throat **(ENT**) signs are present in **70 to 100%** of cases at
- diagnosis.
- These can include crusting rhinorrhea, sinusitis, chronic otitis media, or damage of the facial cartilage with deformities causing saddle nose (resulting in a scooped out or depressed appearance of the nose, , and/or perforation of the nasal septum, the palate or the pinna of the ear.

- **Nasal-sinus involvement** is the **most common manifestation** of GPA, the most common hallmark of the disease, and may be the only sign in the localized forms.
- **Nasal obstruction** with hyposmia or anosmia is often the first symptom.


A
B
C

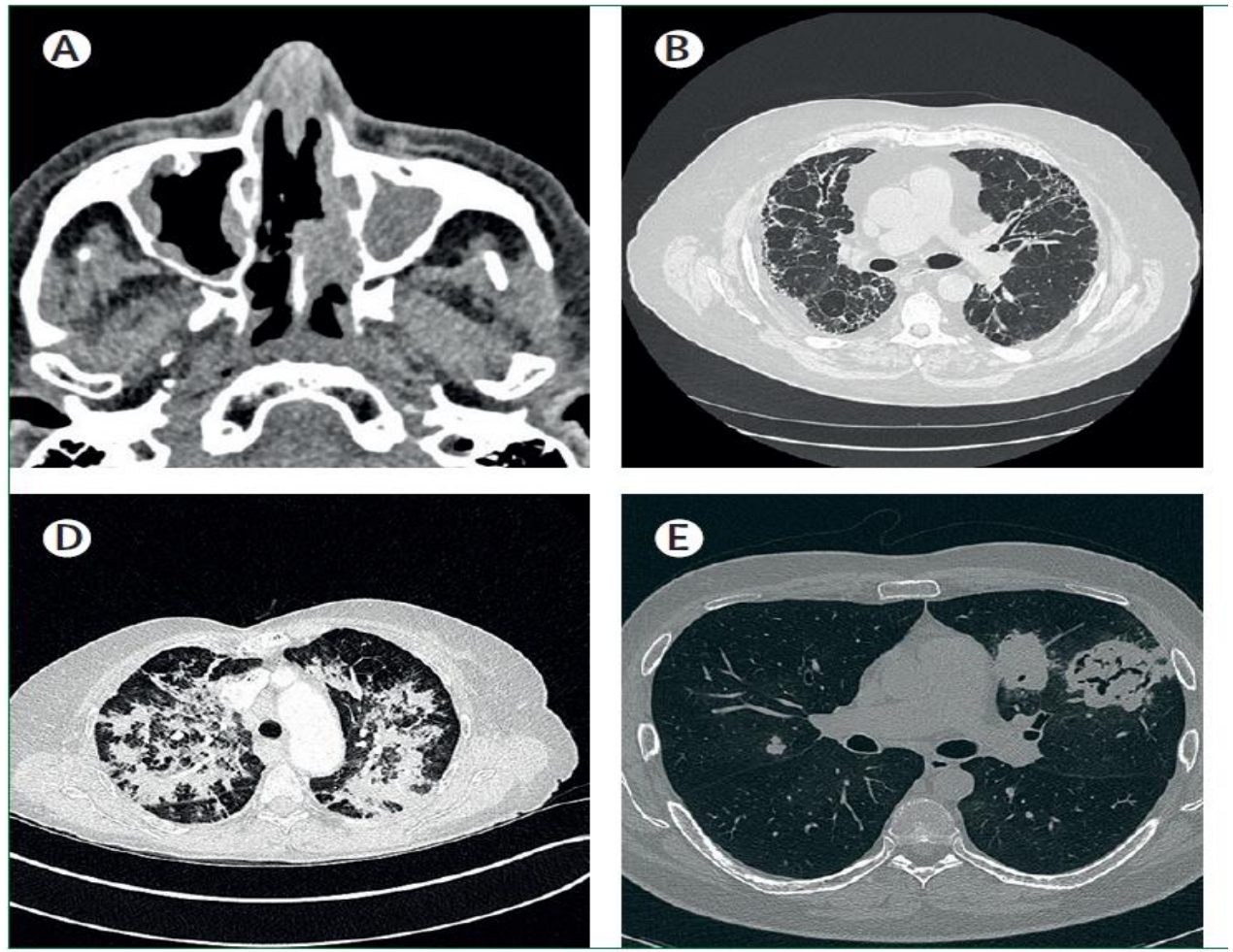


Figure 1: Imaging findings in patients with ANCA-associated vasculitis

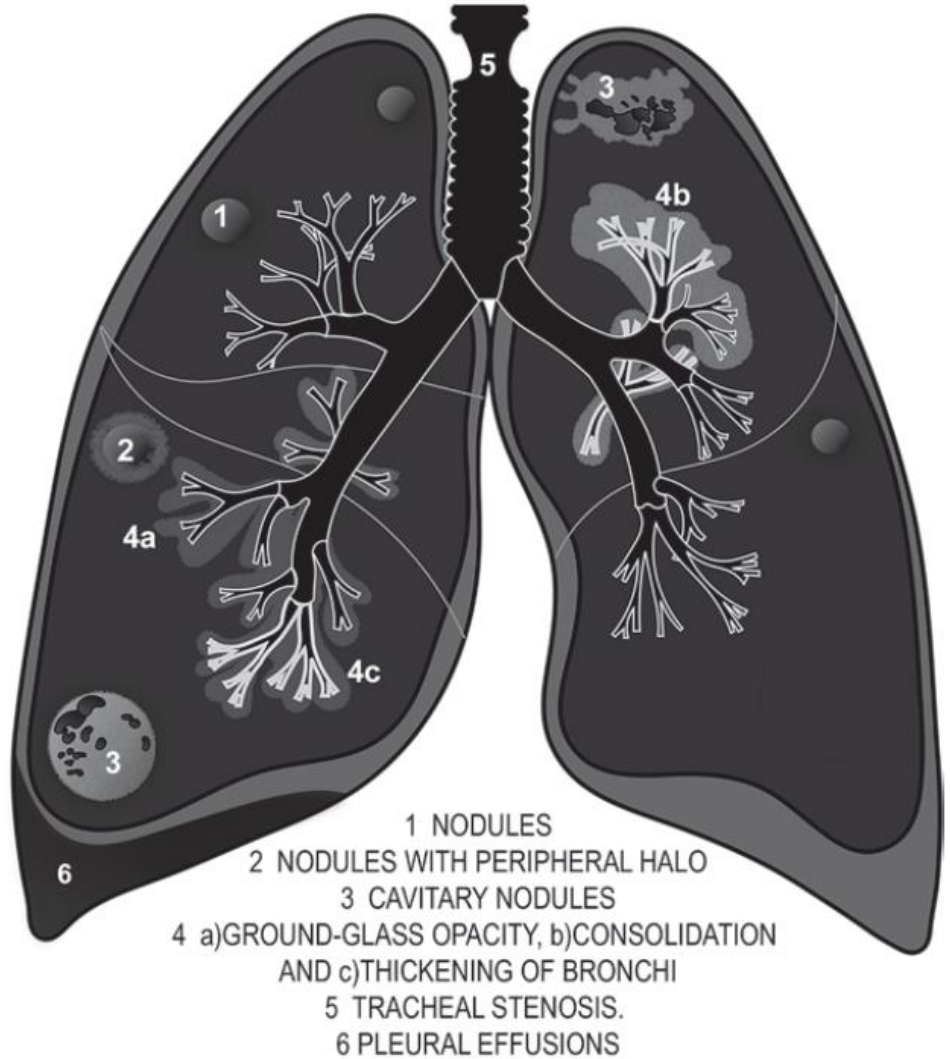
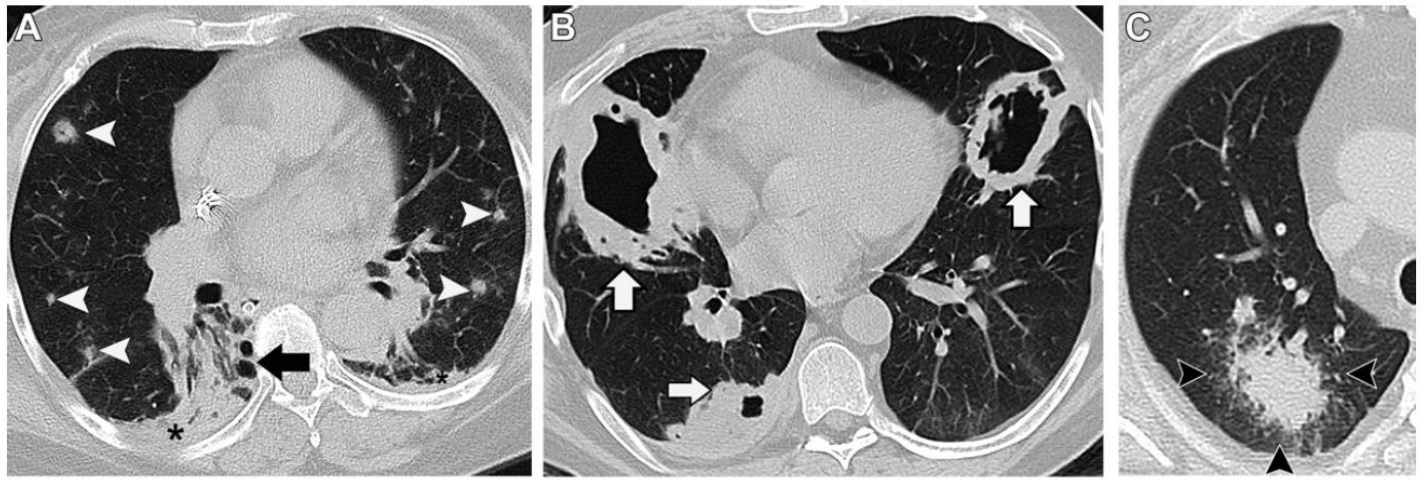


Figure 19. Drawing illustrates the main pulmonary manifestations of GPA.



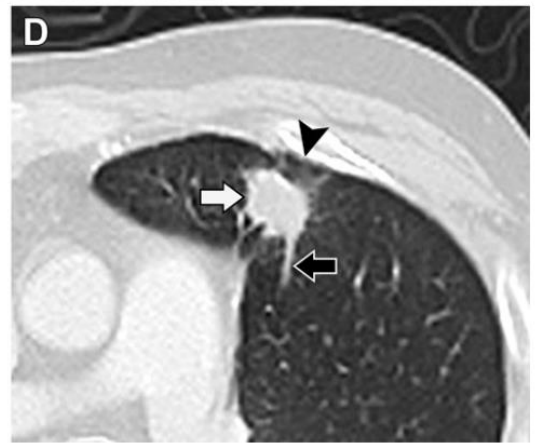


Figure 20. GPA with pulmonary involvement at axial noncontrast CT (lung window) in three patients. **(A)** Image in a 56-year-old woman with a cough shows multiple pulmonary nodules in a random distribution (arrowheads), a right upper lobe consolidation (arrow), and bilateral atelectasis (*). **(B, C)** Images in a 51-year-old man show multiple bilateral cavitary masses with irregular and thick walls measuring more than 2 cm (arrows in **B**), and ground-glass opacity in the right upper lobe (halo sign) (arrowheads in **C**). **(D)** Image in a 42-year-old man with GPA and hemoptysis shows ground-glass opacity (arrowhead) surrounding a consolidated nodule (white arrow) and a pulmonary vessel heading to the nodule in the left superior lobe (feeding vessel sign) (black arrow).

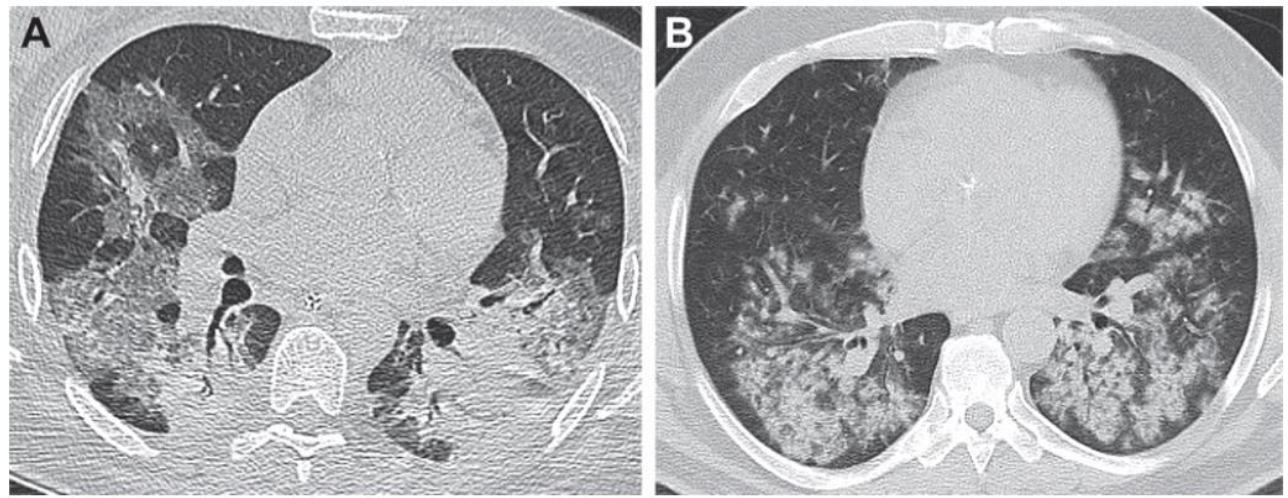


Figure 21. **(A)** Axial noncontrast CT image (lung window) in a 31-year-old woman with a cough and fever shows bilateral diffuse consolidation and ground-glass opacity. **(B)** Axial CT image in a 57-year-old woman with GPA and hemoglobin descent shows diffuse and extensive bilateral ground-glass opacities and consolidations, with sparing of the subpleural lung. Diffuse alveolar hemorrhage was confirmed at bronchoscopy.

- The **most typical renal involvement** is **focal segmental necrotizing** glomerulonephritis associated with **extra capillary proliferation** with **pauci-immune crescent formation** (i.e. without immunoglobulin or complement deposition by immunofluorescence).

- It is the renal damage that **negatively impacts the prognosis** of this disease.

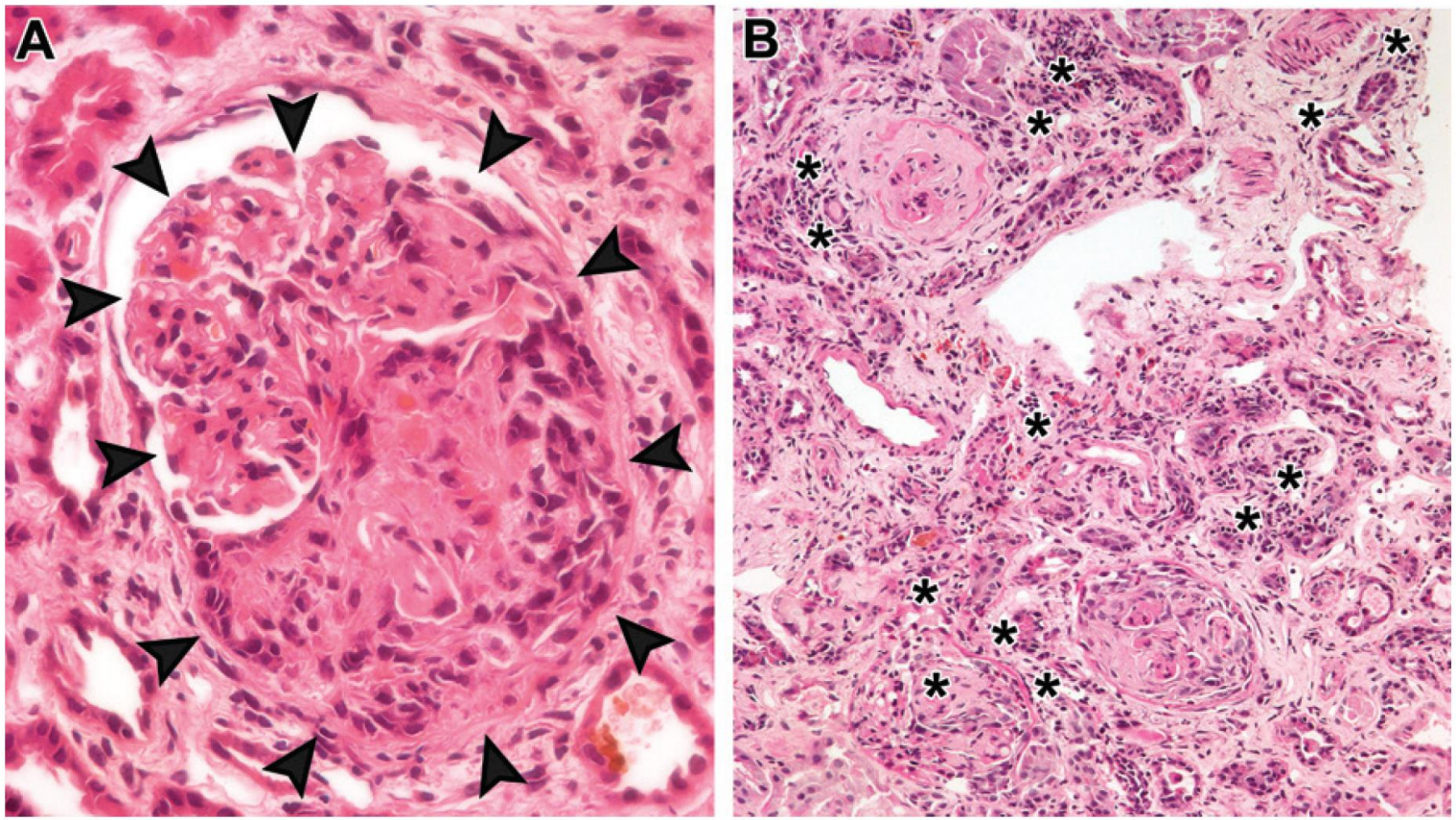


Figure 24. Percutaneous kidney biopsy specimens in a 60-year-old woman with GPA who presented with findings of renal function impairment, active urinary sediment, and subnephrotic proteinuria. **(A)** Photomicrograph (Berden mixed-class renal biopsy) shows pauci-immune necrotizing crescentic glomerulonephritis (arrowheads). (H-E stain; original magnification, ×600.) **(B)** Photomicrograph shows interstitial fibrosis (40%) and moderate tubular atrophy (30%) (*). (H-E stain; original magnification, ×200.)

- The initial glomerular filtration rate (**GFR**) is significantly and independently linked to **mortality.**
- The **kidney biopsy** puncture is done for both the **diagnosis** and the **prognosis** (the number of normal glomeruli on biopsy is an important prognostic factor)

- Urogenital manifestations are **much rarer** and have only been described in men.

- These manifestations can include prostatitis, orchitis, epididymitis, renal pseudotumor, ureteral stenosis, or penis ulceration.

- Involvement of the **peripheral nervous system** affects about **one third** of patients.
- It is characterized by **mononeuritis multiplex** or, less commonly, by **sensorimotor neuropathy**.
- Involvement of the **central nervous system is much rarer (6 to 13%)**
- and may be caused by **granulomatous deposits**, **intracerebral vascular** lesions, or an **extension of sinus lesions**.

- **Pachymeningitis is the most suggestive manifestation**.
- Cases of **granulomatous infiltration** of the pituitary stalk responsible for panhypopituitarism have also been reported.

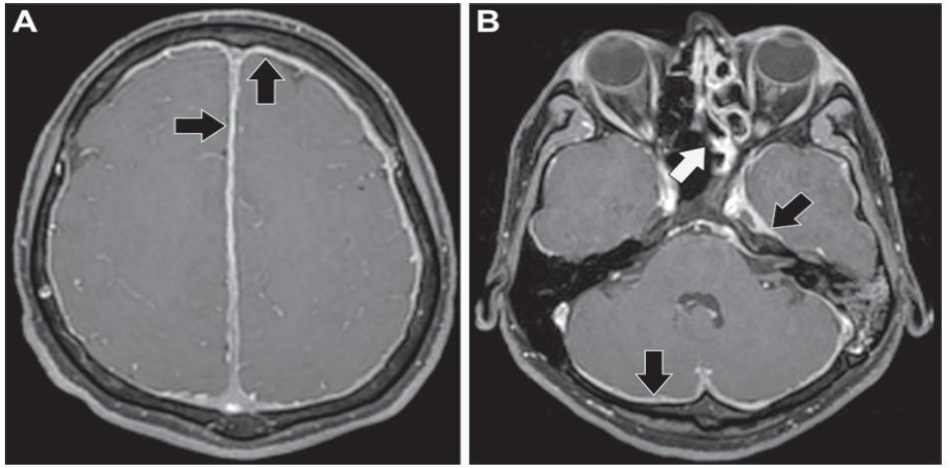


Figure 2. GPA in a 32-year-old man. Axial contrast-enhanced T1-weighted MR images show diffuse pachymeningeal enhancement (black arrows), as well as left ethmoidal sinus disease (white arrow in **B**).

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tients with GPA (19). It is considered a granulomatous manifestation of GPA, being that chronic

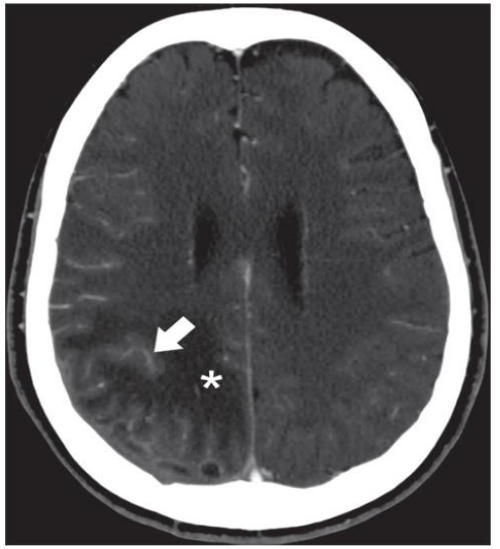
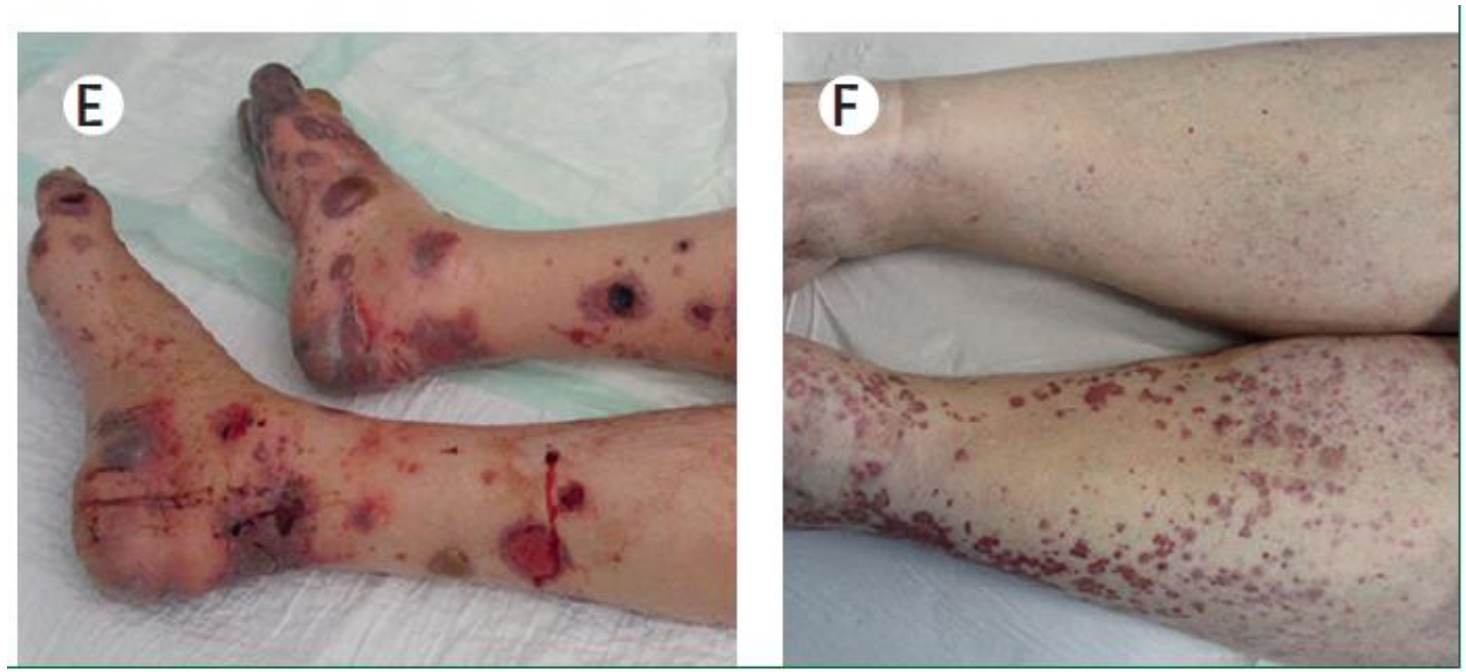


Figure 3. GPA-related leptomeningeal enhancement (arrow) and vasogenic edema (*) on an axial contrast-enhanced CT image in a 34-year-old woman.

RadioGraphics 2021; 41:1973–1991

- Mucocutaneous lesions, mainly **vascular purpura to the lower** limbs,
- are reported in **10 to 50%** of cases ; they can be ulcerating, necrotic
- and widespread.
- There may be **subcutaneous nodules**, **pyoderma gangrenosum**,
- **raspberry-red gingivitis**, and **intraoral and/or genital ulcerations**.


E
F

- **Ocular involvement** occurs fairly frequently (14 to 60%), usually in the
- form of **necrotizing nodular episcleritis**.
- **Scleritis, corneal ulcerations, and retinal vasculitis** also occur.
- Involvement of the eye socket in GPA israrer but can be suggestive of the
- disease, especially when it presents as a **granulomatous retro-orbital pseudotumor** or as **dacryoadenitis**.
- It can be either a primary form or occur secondary to sinus inflammation,
- and it typically manifests as **inflammatory exophthalmia**, which may or
- may not be associated with ophthalmoplegia.

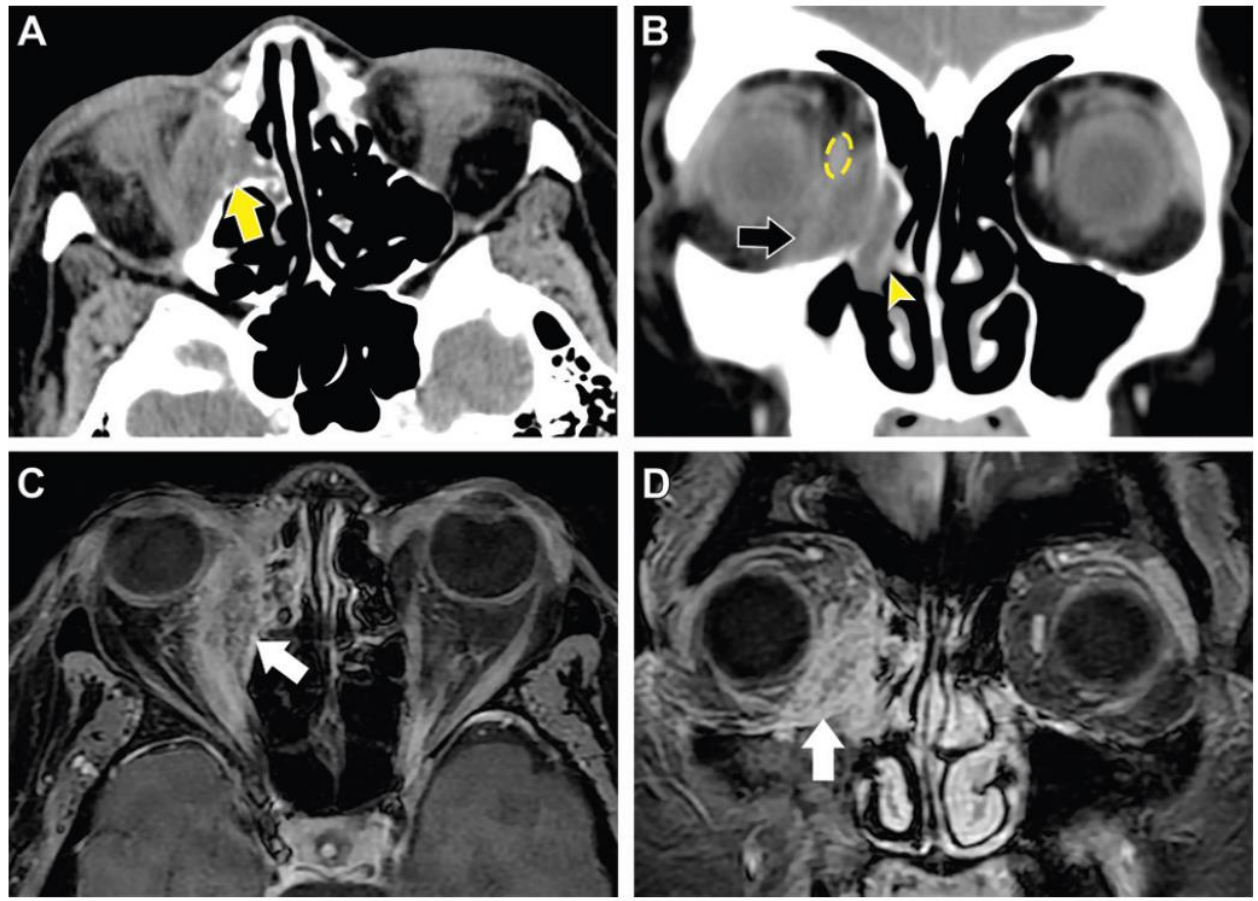


Figure 13. Orbital pseudotumor in a 51-year-old woman. **(A, B)** Axial **(A)** and coronal **(B)** contrast-enhanced CT images show a right orbital soft-tissue lesion with papyraceous lamina destruction (arrow) and obliteration of the middle meatus (arrowhead in **B**). Note the superior displacement of the medial rectus muscle (dashed oval in **B**). **(C, D)** Corresponding axial **(C)** and coronal **(D)** gadolinium-enhanced MR images better depict intense enhancement (arrow).

- **Cardiac involvement is rare** in GPA (**10%**).
- It may be the result of the **vasculitis** or **granulomatous effects** and can occur as **pericarditis, myocarditis, or conduction disorders.**

- The clinical presentation is very heterogeneous, ranging from subclinical manifestations to end-stage heart failure.

- **Gastrointestinal involvement is rare (*5 to 11%*)** and is characterized
- by **ulcerative lesions**, often multiple, as well as **intestinal perforation.**

- Several studies have highlighted a **greater risk of deep vein thrombosis** in patients with GPA, particularly in the active phase of the disease.

- However, the available data do not support the recommendation of systematic preventative anticoagulation in these patients.
-

- At **least 2 different phenotypes** can be distinguished in **GPA ,**
- **with the two forms**
- **localized/limited**
- s**ystemic/diffuse/severe**.
- The localized forms manifest primarily through **ENT involvement**,
- naturally limited to the upper respiratory tract, but they are **recurrent**
- and r**efractory** (known as “grumbling disease”) .
- These localized forms appear to affect a **younger and more female** population

- The **diffuse forms** may manifest through **renal involvement** and/or
- **intra-alveolar hemorrhage (IAH**), and/or the **involvement of at least one vital organ**.

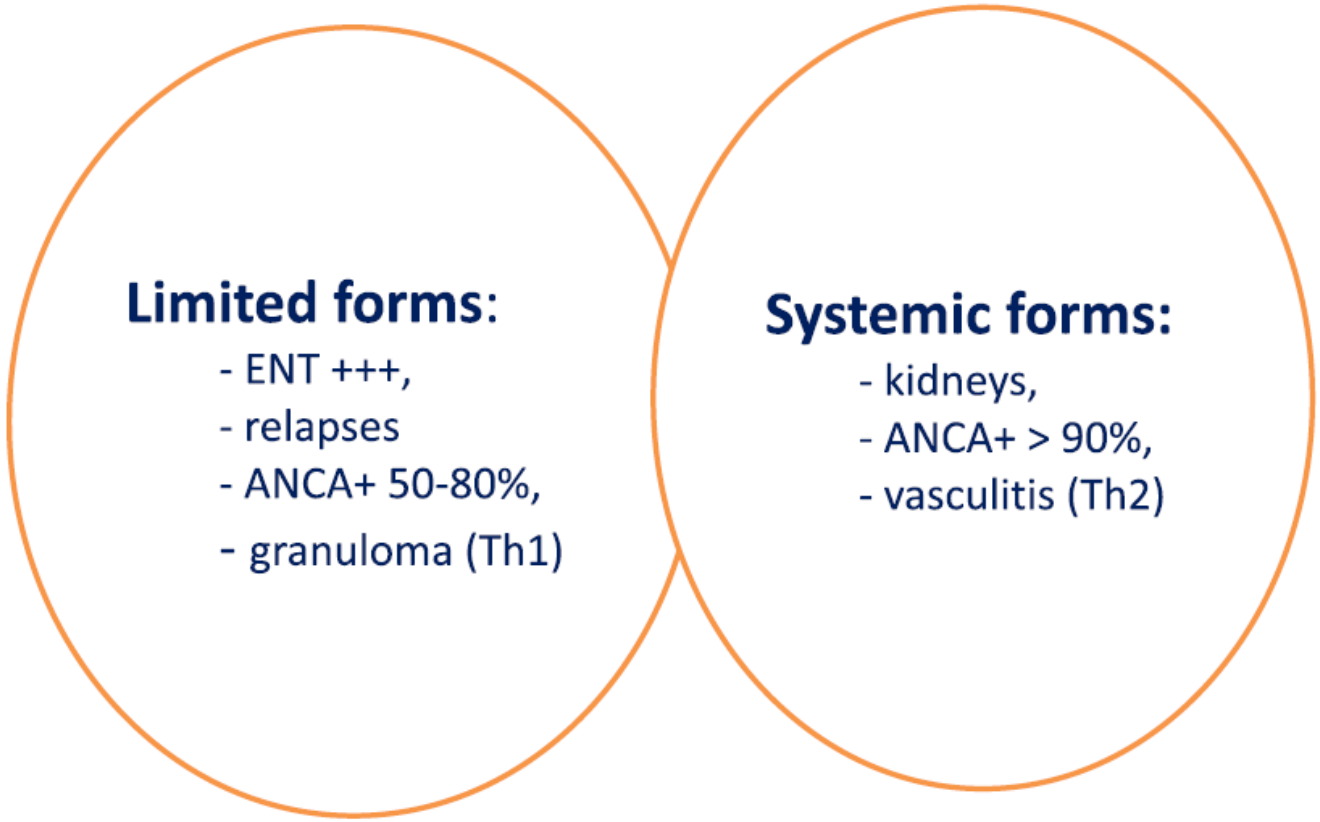


Fig. 3. The different GPA phenotypes.

Autoimmunity Reviews 13 (2014) 1121–1125

Diagnostic yield of biopsies taken from patients with PR3-ANCA-associated vasculitis and MPO-ANCA-associated vasculitis

	Access route or method	Diagnostic yield	Most frequent lesion*	Sampling error issues and aspects to consider
Kidney[14]	Percutaneous	≥99%	Crescentic glomerulonephritis	Low number of glomeruli; atypical lesions (tubulointerstitial nephritis)
Lung[15]	Open	90%	Vasculitic features*	Non-specific inflammation; invasive procedure with a high complication rate
Lung[15]	Transbronchial or CT-guided	≥50%†	Features of mixed inflammatory infiltrate	Biopsy of necrotic areas; complications associated with the procedure (possible pneumothorax)
Ear, nose, and throat[13,16]	Nasal	>30%	Non-specific inflammation and granulomatous or vasculitic features	Inadequate sampling (improve accuracy by taking biopsies >5 mm at the edge of the inflamed area)
Ear, nose, and throat[13,16]	Tracheal-subglottic stenosis	90%	Features of mixed inflammatory infiltrate	Vasculitis features are rare and only present in 10–15% of patients
Eye[17]	Orbit fine needle aspiration or open	>60%	Features of mixed inflammatory infiltrate	Rare disease feature as the eye is generally a non-inflamed area
Skin[18]	Punch biopsy	70–90%	Features of mixed inflammatory infiltrate	Non-specific findings—eg, perivasculitis and acute and chronic inflammation without characteristic features of ANCA-associated vasculitis
Muscle[19]	Open	55–60%	Features of mixed inflammatory infiltrate	More likely positive in women and MPO-ANCA vasculitis

Biopsies taken from other sites are uncommon, but help to differentiate an ANCA-associated vasculitis diagnosis from other pathologies (ie, liver, prostate, or parotid gland diseases). ANCA=antineutrophil cytoplasmic antibody. MPO=myeloperoxidase. PR3=proteinase 3. *Only present in active vasculitis. †The diagnostic yield might have improved over the past decades and depends on the lesion (ie, higher yield when bronchial stenosis and active inflammation is visible). For the biopsy of other lesions, such as pulmonary granulomas, CT-guided biopsy might be preferred.

Table 1: **Diagnostic yield of biopsies taken from patients with PR3-ANCA-associated vasculitis and MPO-ANCA-associated vasculitis**

- Initial assessment of a patient with suspected ANCA-associated vasculitis requires a **systematic approach** to establish the **extent of organ involvement**.

- **Uncommon disease features**, such as **pachymeningitis** and **prostatitis**, shift diagnostic considerations towards infections or malignancies.

- An increase of acute phase reactants, such as the **C-reactive protein**, **erythrocyte sedimentation rate**, and **platelet count**, is found in most patients with active disease.
- **Procalcitonin** concentrations are usually within a normal range in the absence of infection.

- Patients with active ANCA-associated vasculitis also usually present with features of long-standing inflammation, including **anemia of chronic disease**.

- Positive perinuclear (p-ANCA) or cytoplasmic (c-ANCA) patterns detected on **immunofluorescence** studies of serum have substantially **lower predictive values** than positive MPO-ANCA or PR3- ANCA results detected **by enzyme immunoassays**
- Vasculitis, as opposed to a mimic (eg, lupus, sarcoidosis, or an infection), is unlikely if the only serological evidence of ANCA stems from an **indirect immunofluorescence assay** without **confirmation** of PR3-ANCA or MPO-ANCA by immunoassay.

- In **primary AAV**, there is **strong concordance** between **immunofluorescence and immunoassay** results; p-ANCA immunofluorescence corresponds to the presence of MPO-ANCA by immunoassay, and c-ANCA immunofluorescence corresponds to the presence of PR3-ANCA by immunoassay.

- **Discordance across ANCA assays** (eg, c-ANCA immunofluorescence associated with MPO-ANCA positivity) often **suggests a drug-induced** condition.

- **Substantial overlap exists** between the **PR3-ANCA** and **MPO-ANCA** disease subsets.

- **Usual interstitial pneumonia** is a pulmonary finding that almost always occurs in association with **MPO-ANCA-associated vasculitis**, and **cavitary pulmonary nodules are largely exclusive** to patients with **PR3-ANCA-associated vasculitis.**

- There are also **subtle differences in kidney presentations** between the two subsets. Although **histopathological** findings within the kidney **do not permit differentiation** in any given biopsy
- **MPO-ANCA**-associated vasculitis affecting the kidney can have a **slowly progressive phenotype** characterised by **extensive sclerosis** at diagnosis.
- **Rapidly progressive renal decline** is more typical of **PR3-ANCA**-associated vasculitis.
- **More patients with MPO-ANCA-associated** vasculitis **reach end stage** kidney disease or already have advanced kidney damage at presentation.

Classification and epidemiology of vasculitis: Emerging concepts

Tegwen Ecclestone [a], Richard A. Watts [b, *]

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Best practice & Research Clinical Rheumatology37(2023)101845

2020 American College of Rheumatology/European League Against Rheumatism classification criteria for granulomatosis with polyangiitis

Clinical Criteria	Nasal bloody discharge, ulcers, crusting, congestion or blockage, or nasal septal defect /perforation	+3
	Cartilaginous involvement (cartilage inflammation of the ear or nose, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
	Conductive or sensorineural hearing loss	+1
Diagnostic Testing Criteria	cANCA or anti-PR3 ANCA positive	+5
	Pulmonary nodules, mass, or cavitation on chest imaging	+2
	Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
	Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
	Pauci-immune glomerulonephritis on biopsy	+1
	pANCA or anti-MPO ANCA positive	-1
	Serum eosinophil count ≥ 1 ($x10^9$/L)	-4

Sum scores for 10 items, if present. A score of ≥ 5 is needed for classification of granulomatosis with polyangiitis.

- Drug-induced ANCA-associated vasculitis, potentially triggered by several medications, generally **occurs within the first year of exposure** to the causal agent
- Drug-induced ANCA-associated vasculitis is more likely to affect **women** than men, and investigations have reported that **up to 80%** of patients with drug-induced ANCA-associated vasculitis are **female.**
- **Hydralazine**, infrequently used to manage hypertension, and **propylthiouracil** and me**thiamazole** or **carbimazole,** commonly used to treat hyperthyroidism, frequently induce **ANCA positivity in 20%49** of patients taking these drugs.

- **Vasculitis**, however, occurs in only a **minority** of these patients, and they are almost always **MPO-ANCA positive**.
- **Cocaine adulterated with levamisole** is also a common cause of drug-induced vasculitis, and patients with levamisole-induced disease frequently have **necrotizing vasculitis of the skin** that commonly affects the **earlobes.**
- The use of **cocaine itself can lead to midline destructive lesions** of the face with a **high incidence of nasal septal perforation** or **oronasal fistula**, but **systemic involvement is rare in** cocaine-induced granulomatosis with polyangiitis.

- Among **42 patients with cocaine-induced vasculitis**, **discordant immunofluorescence** and enzyme immunoassay results were common.
- **56% of the patients were PR3- ANCA positive**, but none were MPO-ANCA positive.
- screening urine for **cocaine metabolites and levamisole** is useful for establishing true vasculitis versus drug-induced vasculitis in appropriate clinical settings.

- **Immune checkpoint inhibitors**, which exert their effects via activation of the immune system, have also been associated with developing ANCA-associated vasculitis.

- **Drug-induced** vasculitis often presents with **double positivity**—the simultaneous finding of **PR3-ANCA and MPO-ANCA**—or **discordance** between immunofluorescence and enzyme immunoassay results.

- **False-positive ANCA assays** are also found in patients with other **primary autoimmune** disorders,or **secondary to infections** or **malignancies**.

- Infections or malignancies need to be considered as the underlying cause of a false-positive ANCA result in patients with **persistant active** disease despite appropriate ANCA-associated vasculitis **therapy**.

Conditions associated with antineutrophil cytoplasmic antibody (ANCA) other than ANCA-associated vasculitis

Gastrointestinal disorders
Inflammatory bowel disease
Primary sclerosing cholangitis
Primary biliary cirrhosis
Autoimmune hepatitis
Viral hepatitis

Infections
Infective endocarditis
Tuberculosis
Malaria

Drugs
Propylthiouracil
Minocycline
Hydralazine
Allopurinol
Levamisole

Autoimmune diseases
Rheumatoid arthritis
Systemic lupus erythematosus (SLE)[a]
Antiglomerular basement membrane disease

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[a]Antinuclear antibody (ANA) and p-ANCA resemble each other closely and are difficult to differentiate. Thus, SLE sera may show positive p-ANCA staining due to presence of ANA.

Treatment of granulomatosis with polyangiitis and microscopic polyangiitis: induction of remission

- The introduction of cyclophosphamide, an alkylating agent, transformed ANCA-associated vasculitis from a nearly universally fatal condition to one that could be put into temporary remissions in most cases.

Treatment of granulomatosis with polyangiitis and microscopic polyangiitis: induction of remission

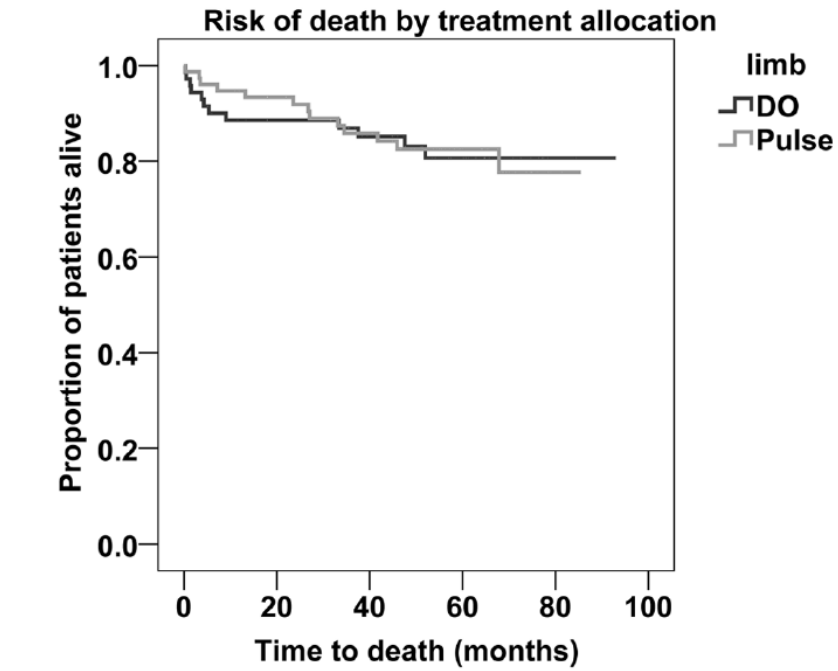
- The CYCLOPS trial compared i**ntravenous** and oral cyclophosphamide administration in generalized ANCA-associated vasculitis and found that the **intravenous regimen** was associated with a **reduction** in cyclophosphamide **exposure by approximately 50%**.

- Nevertheless, almost **88% of patients in both groups** entered **remission by 9 months** after treatment initiation.
- Throughout this follow-up period, disease **relapses occurred in 40%** of those in the **intravenous** cyclophosphamide group, compared with **21% of those in the oral group.**

EXTENDED REPORT

Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up

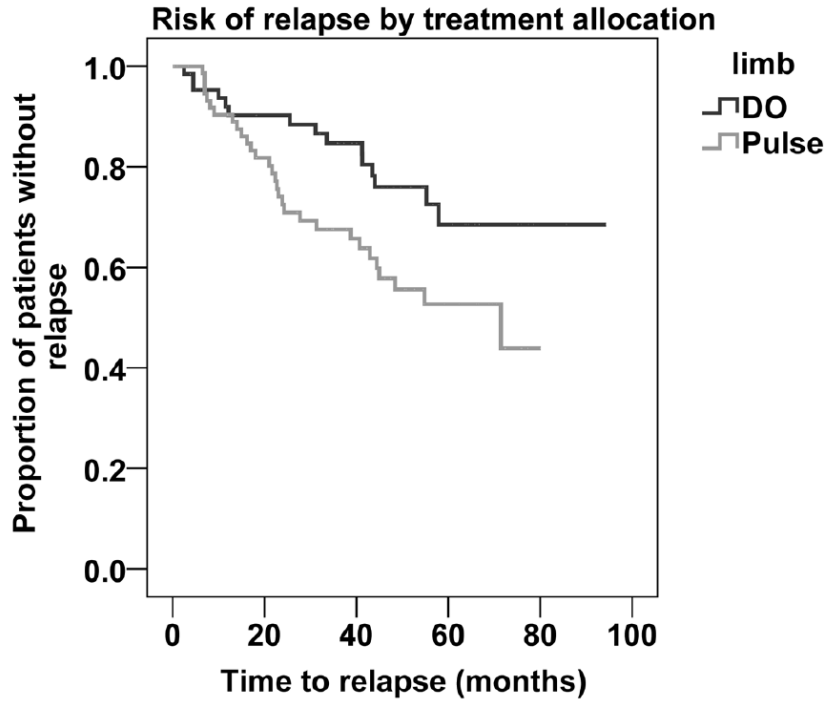
Lorraine Harper,[1] Matthew D Morgan,[1] Michael Walsh,[2] Peter Hoglund,[3] Kerstin Westman,[4] Oliver Flossmann,[5] Vladimir Tesar,[6] Phillipe Vanhille,[7] Kirsten de Groot,[8] Raashid Luqmani,[9] Luis Felipe Flores-Suarez,[10] Richard Watts,[11] Charles Pusey,[12] Annette Bruchfeld,[13] Niels Rasmussen,[14] Daniel Blockmans,[15] Caroline O Savage,[1] David Jayne[1] on behalf of EUVAS investigators



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
Pulse (n)	76	64	54	24	3

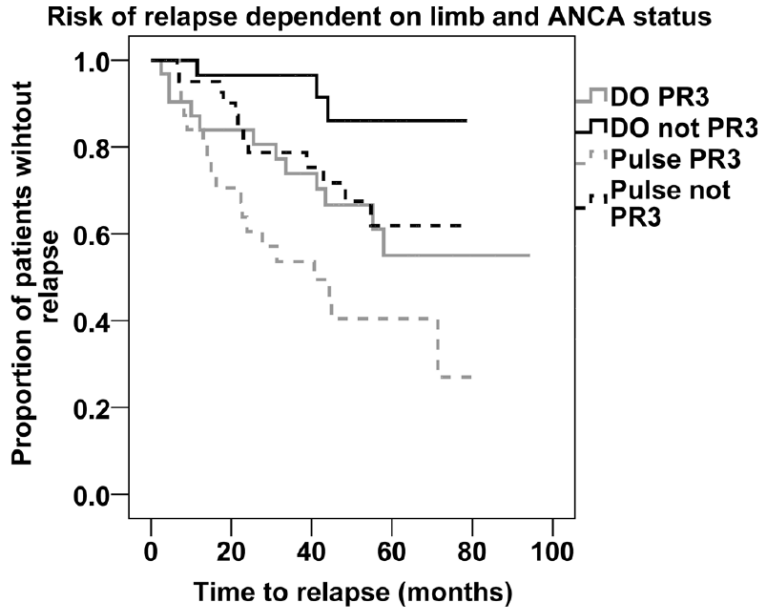
Figure 1. Patient survival according to treatment allocation. There was no significant difference in mortality risk between patients randomised to pulse cyclophsophamide or daily oral (DO) treatment.

Harper L, Morgan MD, Walsh M, *et al*. *Ann Rheum Dis* (2011



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
Pulse (n)	76	64	54	24	3

Figure 2. Relapse-free survival in the two treatment arms. Using Kaplan–Meier survival analysis, there was a significantly increased risk of relapse during follow-up in patients randomised to pulse cyclophsophamide rather than daily oral (DO) treatment (p=0.029).



Time (months)	0	20	40	60	80
DO not PR3-ANCA (n)	39	24	20	8	0
Pulse not PR3-ANCA (n)	43	32	22	9	0
DO PR3-ANCA (n)	33	25	21	9	2
Pulse PR3-ANCA (n)	33	21	13	5	1

Figure 3. Risk of relapse defined by PR3-ANCA status and trial treatment limb. In the multivariable analysis, trial limb and PR3-ANCA status were independent risk factors for relapse. The biological interaction between the two factors can be seen here in the stratification of risk of relapse. PR3-ANCA positive patients receiving

Harper L, Morgan MD, Walsh M, *et al*. *Ann Rheum Dis* (2011

Table 1 Factors associated with relapse in the multivariable analysis

		95.0% CI		
	HR	**Lower**	**Upper**	**p Value**
DO vs pulse	0.46	0.25	0.86	0.015
PR3-ANCA positive vs negative	2.47	1.32	4.59	0.004

ANCA, antineutrophil cytoplasm autoantibodies; PR3-ANCA, antiproteinase 3 antibodies; DO, daily oral.

Table 3 Adverse events. There were no differences between trial treatment limbs in the incidence of adverse events beyond the original trial

	DO (n=60)	Pulse (n=67)
Malignancy	6	8
Severe infection requiring admission to hospital	15	19
Cardiovascular disease	3	6
Cerebrovascular disease	0	2
Venous thrombotic event	6	6
New onset diabetes mellitus	5	8
Fracture	3	6

DO, daily oral.

Harper L, Morgan MD, Walsh M, *et al*. *Ann Rheum Dis* (2011

- If c**yclophosphamide** is used at all, it is **only in short (eg, 3 months**) regimens, and the **long-term regimens** used in the CYCLOPS trial (up to ten pulses) are **discouraged** because of toxicity concerns (eg, malignancy), regardless of the route of administration.

Rituximab-based regimens

- Successful use of rituximab, a chimeric monoclonal antibody targeting CD20+ cells, to treat ANCA-associated vasculitis was first reported in 2001.
- In the RAVE trial, a regimen of **rituximab plus glucocorticoids** was compared with **oral daily cyclophosphamide plus glucocorticoids** for remission induction, to show that the rituximab-based regimen was non-inferior.
- The RAVE protocol stipulated that patients' **concomitant prednisone** treatment was to be tapered to **discontinuation over 5·5 months**.
- **64% of the rituximab group and 53% of the cyclophosphamide (induction) and azathioprine (maintenance) group entered remission** without the use of glucocorticoids, which was the primary endpoint.

ORIGINAL ARTICLE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D.,

Neurologic involvement (%)	25	15	0.08
Cranial-nerve palsy	0	1	0.50
Meningitis	1	0	0.50
Motor mononeuritis multiplex	11	9	0.20
Sensory peripheral neuropathy	22	13	0.10
ANCA-positive at diagnosis (%)			
By immunofluorescence			
All	98	96	
C-ANCA	66	62	
P-ANCA	33	34	
By ELISA			
All	98	100	
Proteinase 3 ANCA	67	66	
Myeloperoxidase-ANCA	32	34	
Mean dose of glucocorticoids from 14 days before consent provided to first infusion of study drug			
Methylprednisolone (g)	0.8±1.28	0.7±1.10	
Prednisone (mg)	253.6±236.5	296.1±266.2	

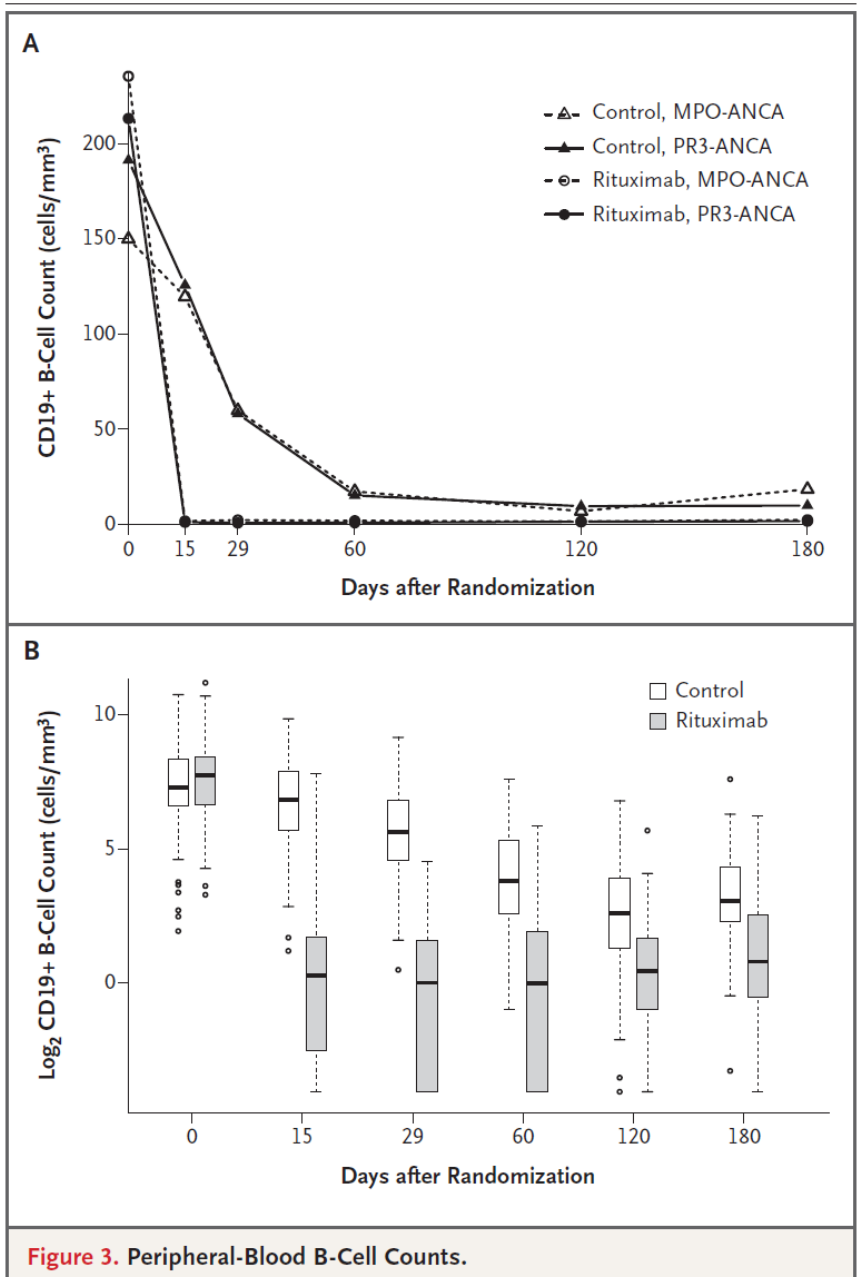


Figure 3. Peripheral-Blood B-Cell Counts.

- Control=98
- Rituximab=99
- Remission induction : 39%Rituximab, 33%CYC
- Exclusion criteria: Cr>4
- Alveolar hemorrhage with ventilator support

- In addition, the **rituximab group** showed **non-inferiority** to the cyclophosphamide and azathioprine group for **remission induction** ($p<0{\cdot}001$) and fell just short of statistical significance for superiority ($p=0{\cdot}09$).

- Among the patients **with PR3-ANCA-associated** vasculitis, rituximab was **superior for remission induction** and disease recurrence was higher, a finding observed consistently across multiple studies.

- **Cumulative glucocorticoid exposure during 18 months** of follow-up was **not statistically different** between the groups (4·6 g exposure in the rituximab group, 5·1 g exposure in the cyclophosphamide group) and equated to mean daily doses of 8·4 mg and 9·3 mg, respectively, still a substantial burden.

JAMA Network

QUESTION Is a reduced-dose glucocorticoid plus rituximab regimen noninferior to the conventional high-dose glucocorticoid plus rituximab regimen in remission induction of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis?

CONCLUSION This clinical trial found that in patients with newly diagnosed ANCA-associated vasculitis, a reduced-dose glucocorticoid plus rituximab regimen was noninferior to a high-dose glucocorticoid plus rituximab regimen with regard to induction of disease remission.

POPULATION

80 Women
54 Men

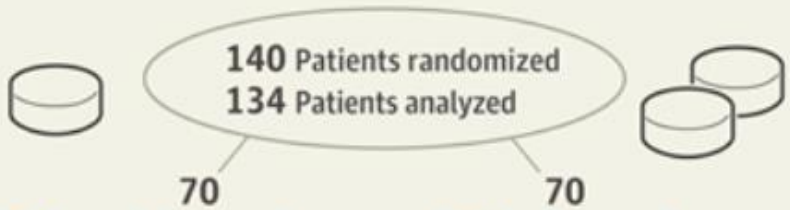
Adults with newly diagnosed ANCA-associated vasculitis without severe glomerulonephritis or alveolar hemorrhage

Median age: 73 years

LOCATIONS

21
Hospitals in Japan

INTERVENTION



Reduced-dose regimen
Reduced-dose prednisolone, 0.5 mg/kg/d, plus rituximab, 375 mg/m²/wk (4 doses)

High-dose regimen
High-dose prednisolone, 1 mg/kg/d, plus rituximab, 375 mg/m²/wk (4 doses)

PRIMARY OUTCOME

Remission rate at 6 months, and the prespecified noninferiority margin was −20 percentage points

FINDINGS

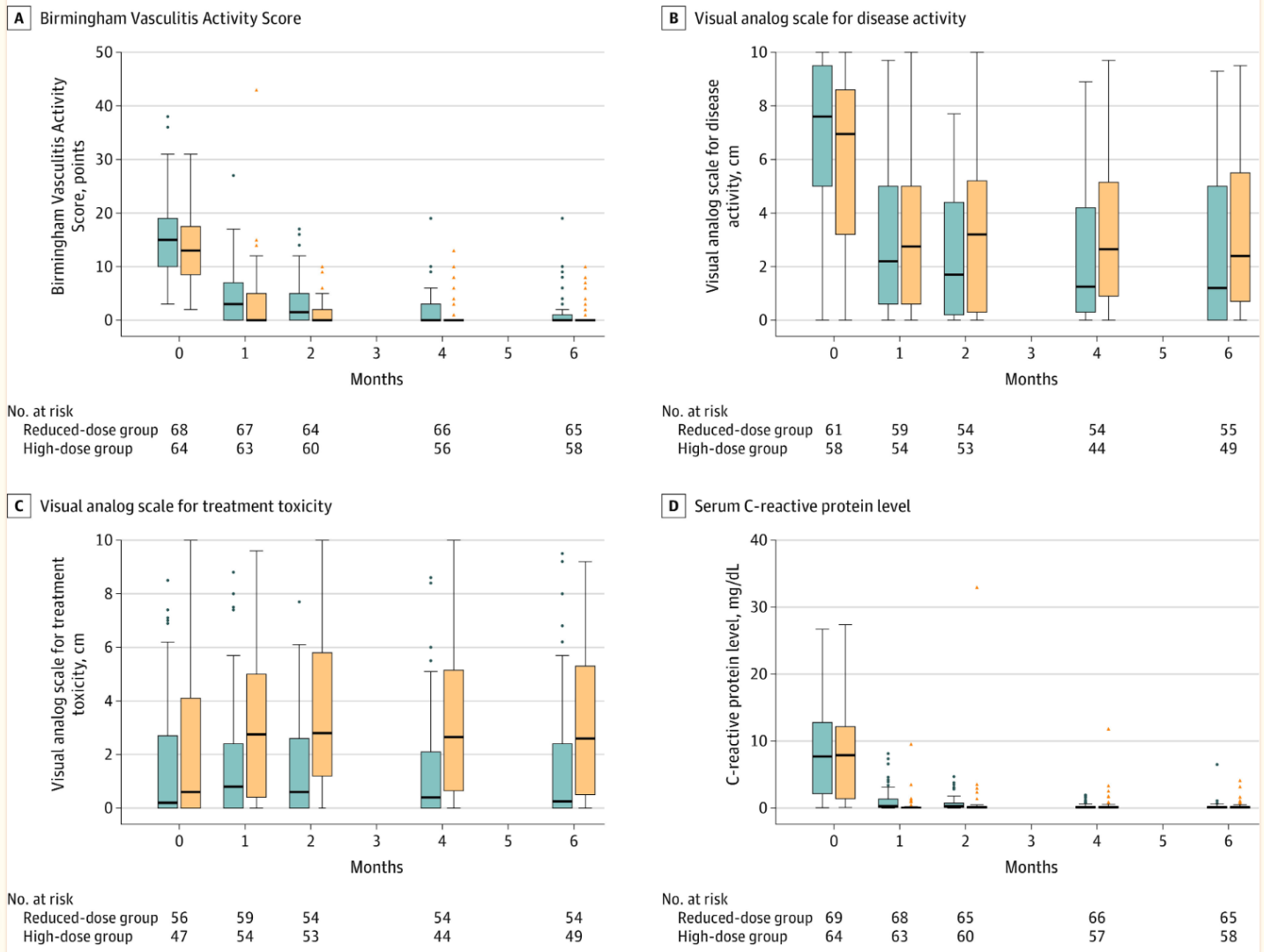
Remission rate at 6 months

Reduced-dose regimen
49 of 69 patients

High-dose regimen
45 of 65 patients

Absolute difference,
1.8 percentage points
(1-sided 97.5%, −13.7 to ∞)

Furuta S, Nakagomi D, Kobayashi Y, et al; LoVAS Collaborators. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: a randomized clinical trial. *JAMA*. Published June 1, 2021. doi:10.1001/jama.2021.6615


A Birmingham Vasculitis Activity Score
Birmingham Vasculitis Activity Score, points
50
40
30
20
10
0
0 1 2 3 4 5 6
Months
No. at risk
Reduced-dose group 68 67 64 66 65
High-dose group 64 63 60 56 58
B Visual analog scale for disease activity
Visual analog scale for disease activity, cm
10
8
6
4
2
0
0 1 2 3 4 5 6
Months
No. at risk
Reduced-dose group 61 59 54 54 55
High-dose group 58 54 53 44 49
C Visual analog scale for treatment toxicity
Visual analog scale for treatment toxicity, cm
10
8
6
4
2
0
0 1 2 3 4 5 6
Months
No. at risk
Reduced-dose group 56 59 54 54 54
High-dose group 47 54 53 44 49
D Serum C-reactive protein level
C-reactive protein level, mg/dL
40
30
20
10
0
0 1 2 3 4 5 6
Months
No. at risk
Reduced-dose group 69 68 65 66 65
High-dose group 64 63 60 57 58

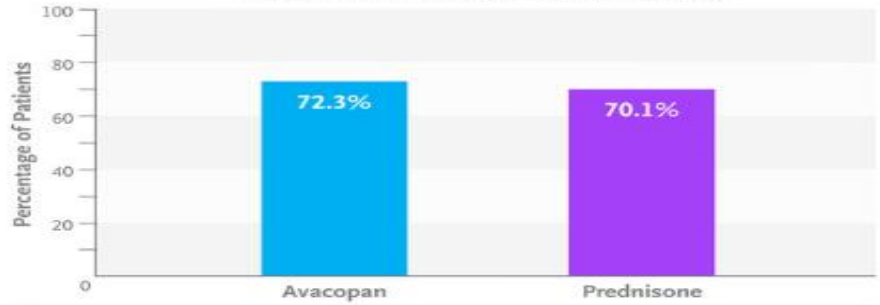
Avacopan

- Avacopan, a small molecule inhibiting the C5a receptor (C5aR1), was approved by the US Food and Drug Administration as an adjunctive therapy for remission induction in 2021.

- In the ADVOCATE trial, patients received a mean daily glucocorticoid dose of **47 mg in the avacopan group and 52 mg in the prednisone** group in the 2 weeks before randomisation and **up to 20 mg/day of prednisone at randomisation.**
- The baseline prednisone treatment in the **avacopan** group was tapered to **discontinuation within 4 weeks** .
- The **control group received a glucocorticoid regimen that was tapered to discontinuation by 20 week**s.
- Avacopan (or placebo) treatment was continued until week 52.

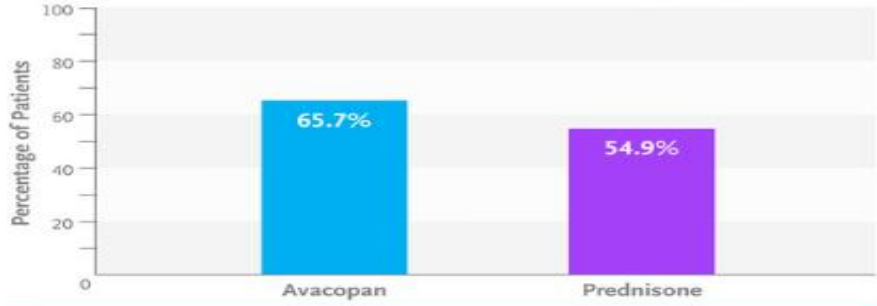
Clinical Remission at Week 26

Estimated common difference, 3.4 percentage points
95% CI, −6.0 to 12.8
P<0.001 for noninferiority; P=0.24 for superiority

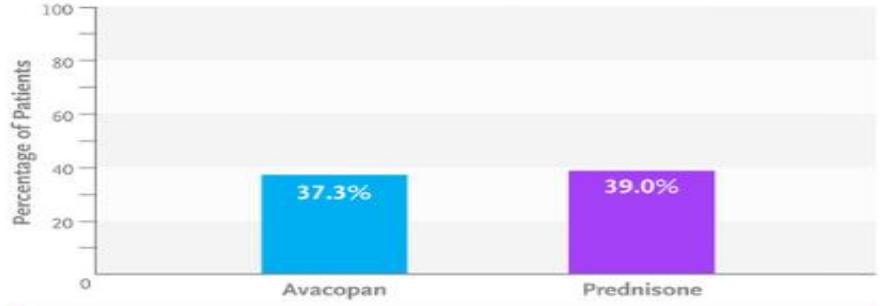


Sustained Remission at Week 52

Estimated common difference, 12.5 percentage points
95% CI, 2.6 to 22.3
P<0.001 for noninferiority; P=0.007 for superiority

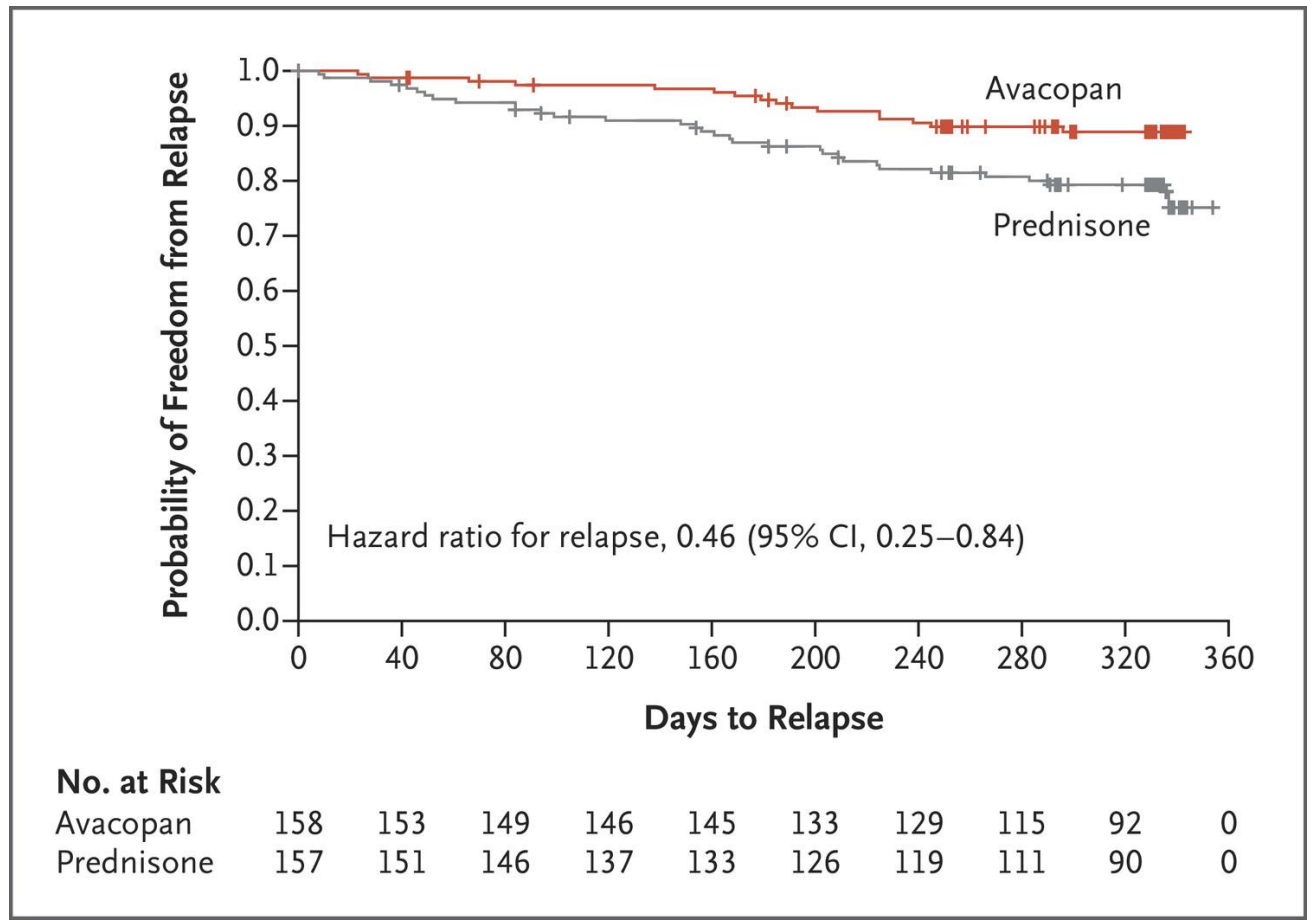


Incidence of Serious Adverse Events
(aside from worsening vasculitis)



CONCLUSIONS

Among patients with ANCA-associated vasculitis, avacopan was noninferior to prednisone with respect to remission at 26 weeks and was superior with respect to sustained remission at 52 weeks.



No. at Risk

Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0

KI REPORTS
KIReports.org

CLINICAL RESEARCH

Renal Recovery for Patients with ANCA-Associated Vasculitis and Low eGFR in the ADVOCATE Trial of Avacopan

Frank B. Cortazar[1], John L. Niles[2], David R.W. Jayne[3], Peter A. Merkel[4], Annette Bruchfeld[5,6], Huibin Yue[6], Thomas J. Schall[6], Pirow Bekker[6] and on behalf of the ADVOCATE Study Group[7]

Renal Recovery for Patients With ANCA-Associated Vasculitis and Low eGFR in the ADVOCATE Trial of Avacopan

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

ADVOCATE trial

Post hoc analysis

Patients with ANCA - associated vasculitis

eGFR ≤20mL/min/1.73m^2
N = 50

Intervention

Prednisone group

n = 23

52 weeks follow-up

Avacopan group

n = 27

Results

	Baseline eGFR mL/min/1.73m^2	Change in eGFR mL/min/1.73m^2	Increase in eGFR of ≥2-fold (%)
Prednisone group	17.5	7.7	13.0
	P = 0.846	P = 0.003	P = 0.030
Avacopan group	17.6	16.1	40.7

ANCA, antineutrophil cytoplasmic antibody

KI REPORTS
Kidney International Reports

Cortazar F et al, 2023

Visual abstract by:
Denisse Arellano, MD
@deniise_am

Conclusion Among patients with baseline eGFR ≤20 mL/min/1.73m^2 in the ADVOCATE trial, eGFR improved more in the avacopan group vs. the prednisone group.

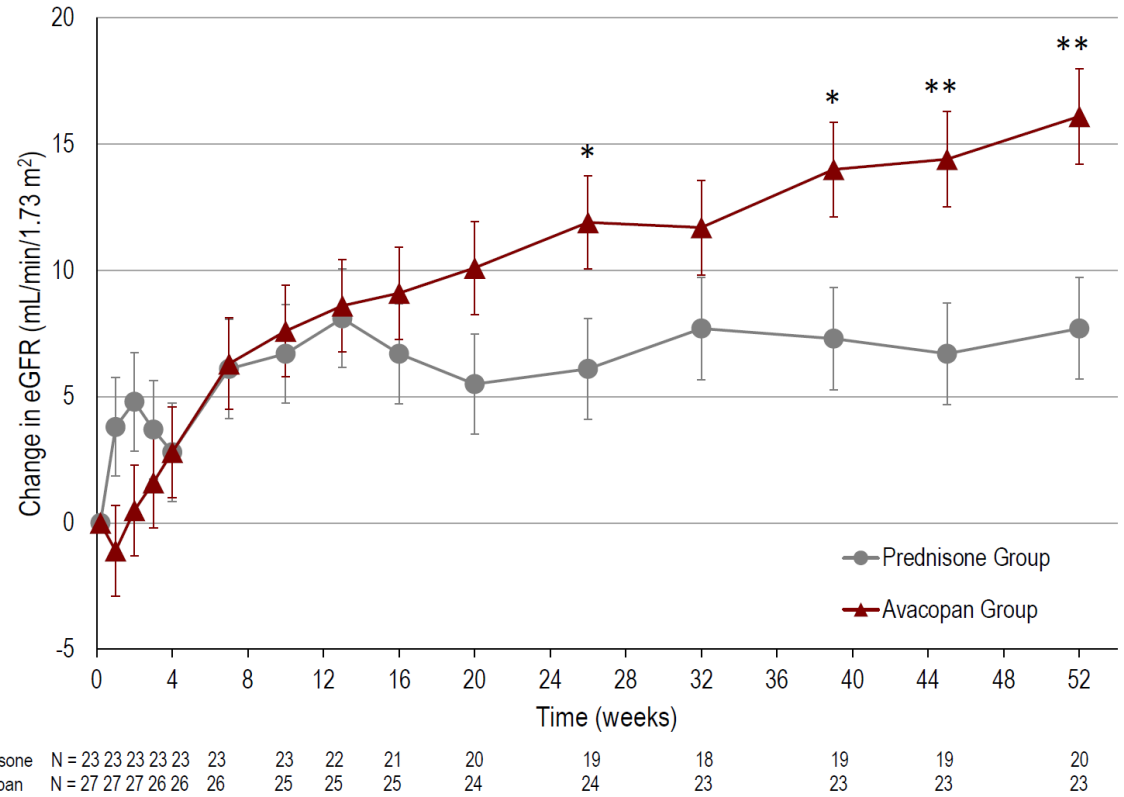


Figure 2. Change in kidney function among patients in the ADVOCATE trial with baseline eGFR ≤20 ml/min per 1.73 m^2. Least squares mean (± SEM) change from baseline in eGFR by treatment group over the 52-week treatment period. *$P < 0.05$, **$P < 0.01$ for comparison of the avacopan group to prednisone group by mixed effects model for repeated measures analysis with treatment group, study visit, and treatment-by-visit interaction as factors, and baseline as covariate. eGFR, estimated glomerular filtration rate.

Kidney International Reports (2023) 8, 860–870

Plasma exchange

- The role of plasma exchange remains debated in the management of ANCA-associated vasculitis.
- Results of the MEPEX trial, a study published in 2007, suggested that the addition of plasma exchange reduced the risk of end-stage kidney disease at 12 months compared with a regimen that used intravenous methylprednisolone pulses
- However, the mortality rate during the first year was high in both groups: 27% in the plasma exchange group and 24% in the intravenous methylprednisolone group. These high fatality rates were more often due to infectious complications than to features of active disease or comorbidities of vasculitis.80

- The randomised (but unblinded) PEXIVAS study included 286 patients with PR3-ANCA-associated vasculitis and 418 patients with MPO-ANCA-associated vasculitis, and had a composite primary endpoint: end stage kidney disease or death
- Both outcomes are complications of ANCA-associated vasculitis that often do not occur for at least several years, if they do occur. By contrast, positive effects of plasma exchange for a severe pulmonary renal syndrome are often seen within the first few weeks after treatment initiation.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, C.D. Pusey, A.L. Casian, B. Brezina, A. Mazzetti, C.A. McAlear, E. Broadhurst, D. Reidlinger, S. Mehta, N. Ives, and D.R.W. Jayne, for the PEXIVAS Investigators*

Table 2. Primary Composite Outcome with Plasma Exchange as Compared with No Plasma Exchange.*

Analysis	Plasma Exchange	No Plasma Exchange	Hazard Ratio (95% CI)
	no. with outcome/total no. (%)		
Primary analysis†	100/352 (28.4)	109/352 (31.0)	0.86 (0.65–1.13)
Partially adjusted analysis‡	100/352 (28.4)	109/352 (31.0)	0.89 (0.68–1.17)
Per-protocol analysis	95/338 (28.1)	99/322 (30.7)	0.85 (0.64–1.13)
Analysis at 1-year follow-up	70/352 (19.9)	85/352 (24.1)	0.77 (0.56–1.06)

* The primary composite outcome was death or end-stage kidney disease in patients with severe ANCA-associated vasculitis. CI denotes confidence interval.
† The primary analysis was adjusted with the use of a model fitted with trial-group assignments and minimization strata as covariates.
‡ The partially adjusted analysis used a model fitted only with trial-group assignments as covariates.

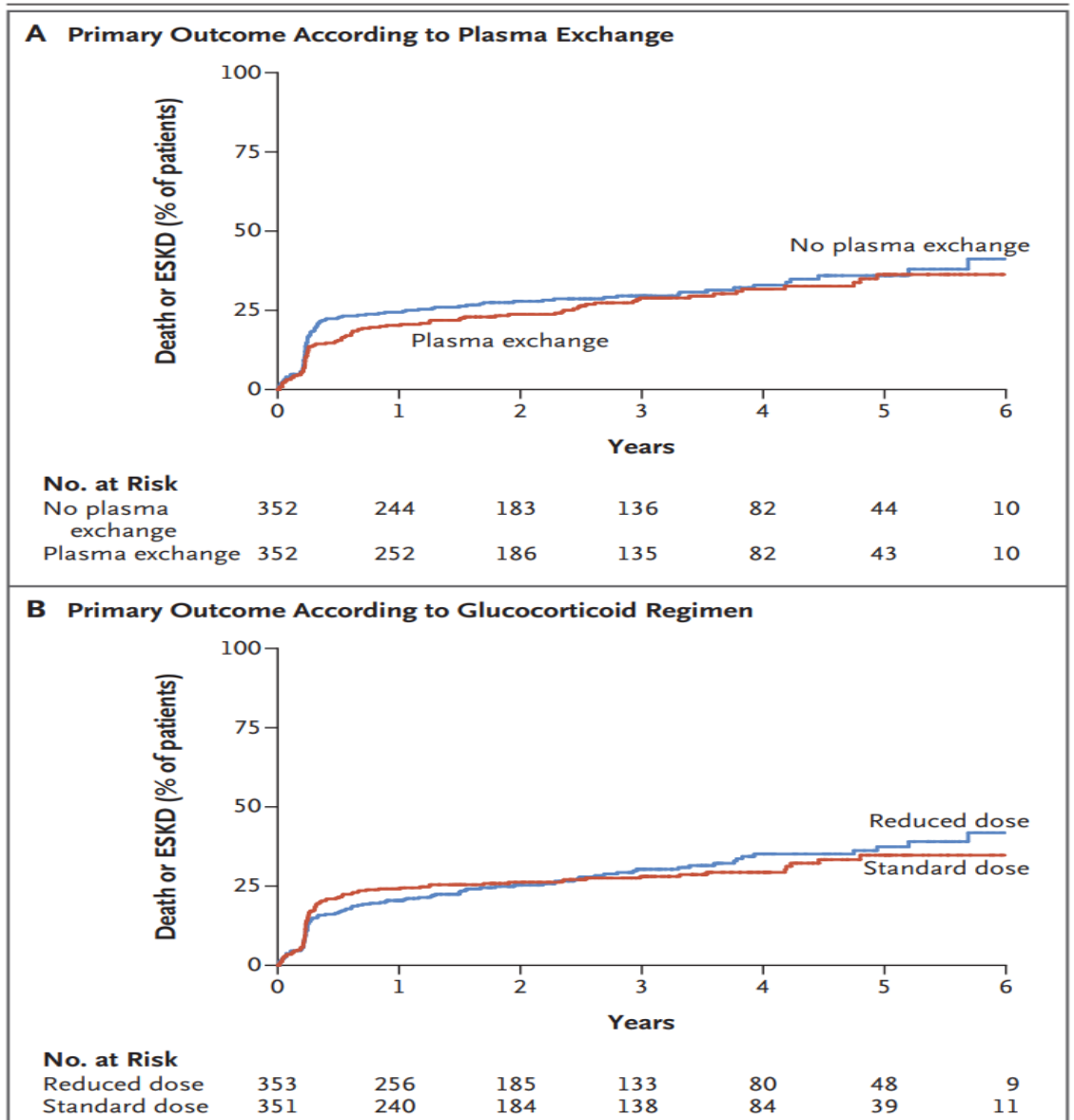
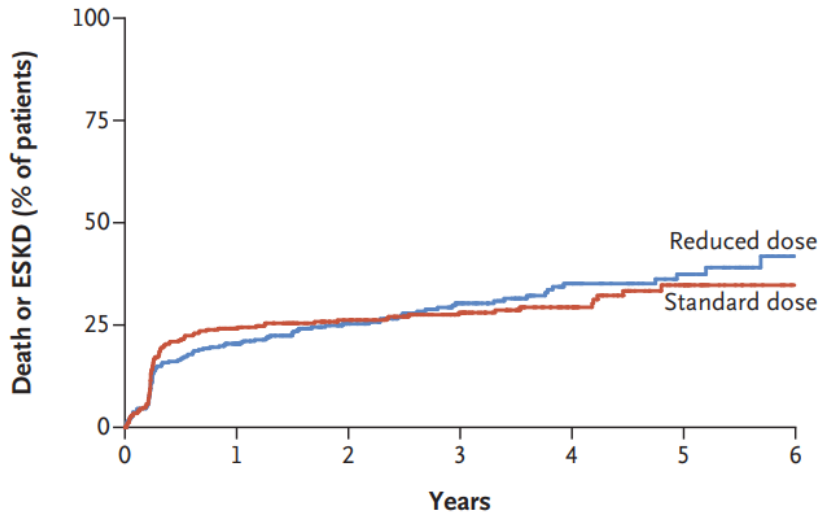


Figure 1. Kaplan–Meier Curves for the Primary Outcome.

The primary composite outcome was death from any cause or end-stage kidney disease (ESKD). In a trial with a 2-by-2 factorial design, patients with

B **Primary Outcome According to Glucocorticoid Regimen**



No. at Risk

Reduced dose	353	256	185	133	80	48	9
Standard dose	351	240	184	138	84	39	11

Figure 1. Kaplan–Meier Curves for the Primary Outcome.

The primary composite outcome was death from any cause or end-stage kidney disease (ESKD). In a trial with a 2-by-2 factorial design, patients with severe antineutrophil cytoplasm antibody–associated vasculitis were assigned to undergo plasma exchange or no plasma exchange (Panel A) and to follow either a reduced-dose regimen or a standard-dose regimen of oral glucocorticoids (Panel B).

- The **primary endpoint in PEXIVAS** of **end stage kidney disease** or **death** was reached by **28%** and **31%** of patients in the **plasma exchange** and **control groups**, respectively, over a mean follow-up of **2·9 years** (p=0·27).
- These results did not cause many clinicians to change their opinions about the role of plasma exchange, and those who did not endorse plasma exchange before the trial cited it as evidence that the therapy is not worthwhile.82

- **A meta-analysis** incorporating trial data collected over four decades reported that patients with a serum creatinine concentration greater than or equal to **3·4 mg/dL have a reduced likelihood of developing end stage kidney disease at 1 year if plasma exchange** is added to standard therapy.

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

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

BMJ 2022;376:e064604

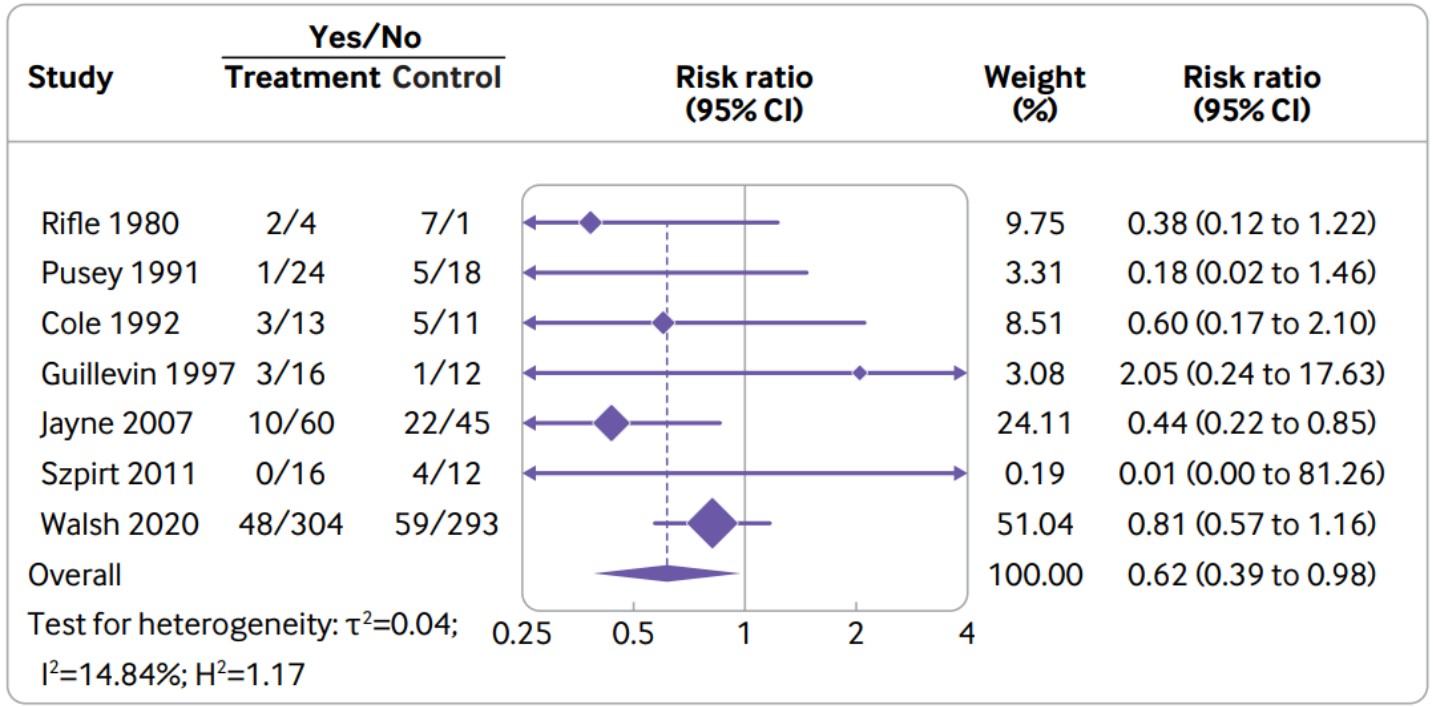


Fig 3 | Effect of plasma exchange on end stage kidney disease within 12 months' follow-up in patients with anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis using the DerSimonian and Laird random effects mode with Knapp-Hartung standard error adjustment

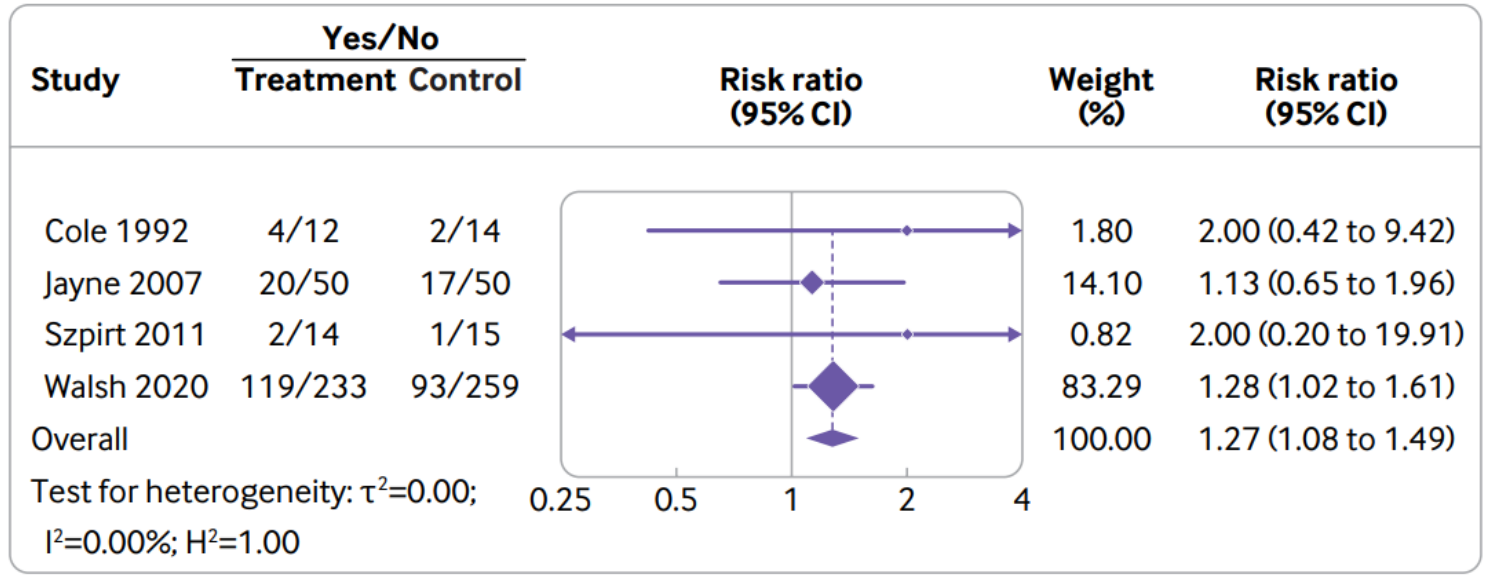


Fig 4 | Effect of plasma exchange on serious infection within 12 months' follow-up in patients with anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis using the DerSimonian and Laird random effects model with Knapp-Hartung standard error adjustment

- The use of plasma exchange therefore remains a centre-based decision, and if it is to be used, it **should probably be done early in** the treatment course of patients with **severe disease** and should be administered at **experienced institutions** that are adept at mitigating the substantial risk of infection.

Methotrexate

- Methotrexate is given to induce remission in patients for whom other **treatments** are **contraindicated, undesired, poorly tolerated**, or **inaccessible.**
- It was **often given to patients with limited granulomatosis with polyangiitis** (panel) from 1992 to 2010,86 but **its use has declined** substantially since the approval of rituximab for remission induction in 2011.
- Methotrexate appears to be effective for remission induction when used with glucocorticoids, but was never tested in a clinical trial combined with glucocorticoids against a treatment group of glucocorticoids alone.
- The likelihood of disease flare following the discontinuation of prednisone appears to be high.

- Nevertheless, in some clinical scenarios (eg, the height of the COVID-19 pandemic), methotrexate might be a useful part of a remission induction regimen for patients who **do not have severe ANCA-associated** vasculitis.
- The drug dose should be **reduced** in patients with **chronic kidney** disease and **should not be given at all to patients with an eGFR less** than or equal to **30 mL/min per 1·73m²** because of a heightened risk of methotrexate toxicity in that setting

- All patients undergoing remission induction regimens should receive prophylaxis with trimethoprim plus sulfamethoxazole (TMP plus SMX) or another appropriate **antibiotic regimen during remission induction**.

- **TMP plus SMX** is effective not only in preventing ***Pneumocystis jirovecii*** infection, but also in reducing the **incidence of bacterial infections** in patients with ANCA-associated vasculitis receiving treatment.

- In summary, trends in remission induction strategies in ANCA-associated vasculitis over the past two decades have diverged from reliance on cyclophosphamide for patients with generalised disease, **in favour of rituximab**.
- **Shorter glucocorticoid** courses and regimens designed to reduce and taper glucocorticoids completely have also been emphasised, although it is probable that clinicians in practice still rely too heavily on them.
- **Avacopan** is an essential adjunct for remission induction and could decrease the length of glucocorticoid exposure substantially

Maintenance of remission

- Since 2021, guidelines and recommendations issued by the American College of Rheumatology/Vasculitis Foundation (ACR/VF)91 and the European Alliance of Associations for Rheumatology (EULAR) recommend the use of **rituximab as the first-line agent for remission maintenance**.

- The **MAINRITSAN1 trial** randomised patients who were newly diagnosed or relapsing to either **rituximab** or **azathioprine** following induction therapy with cyclophosphamide.
- **Major relapses occurred in 5% (rituximab**) versus **29% (azathioprine**) of patients during a follow-up of 28 months, and the safety profiles of the two treatment regimens were comparable

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 6, 2014 VOL. 371 NO. 19

Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

RITAZAREM: Rituximab Versus Azathioprine for Maintenance of Remission for Patients With ANCA-associated Vasculitis and Relapsing Disease: An International Randomised Controlled Trial

#NephJC

Study Design

RITAZAREM trial had 3 phases

Induction phase (0-4 months)
RTX (4x 375 mg/m²/week)
and oral prednisone (high or low-dose)

Maintenance phase (4–24 months)
Patients who had achieved remission
1. BVAS/WG ≤1
2. and prednisone ≤10 mg/day

Randomized to RTX or AZA

Follow-up phase (36–48 months)
Off-treatment phase

Patients

Inclusion Criteria

- GPA or MPA diagnosis
  Current/prior positive PR3 or MPO
- Patients age >15 years
- Disease relapse after remission
  defined by 1 major or 3 minor disease activity items on BVAS/WG

Exclusion Criteria

- Other multisystem autoimmune diseases

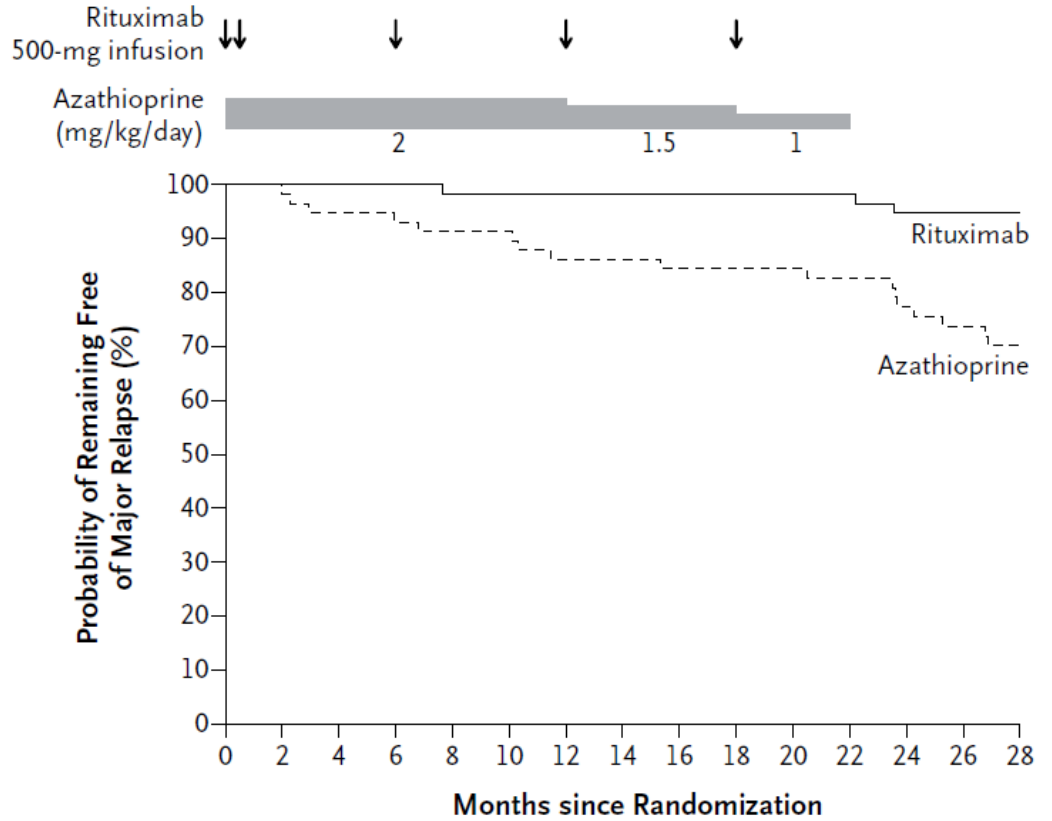
Smith, Rona M et al. "Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial." *Annals of the rheumatic diseases*, ard-2022-223559. 23 Mar. 2023

@HusamJZ

Figure 2. Kaplan–Meier Curves for the Probability of Remaining Free of Relapse According to Treatment Group.

Patients were randomly assigned to receive maintenanc 0 and 14 a st infusion am per day from month 0 to 12, 1.5 mg per kilogram per day until month 18, then 1 mg per kilogram per day until the last day of month 22 [horizontal gray bars]). Panel A shows the probability of remaining free of major relapse after randomization. The hazard ratio for major relapse for patients in the azathioprine group, as compared with rituximab recipients, was 6.61 (95% CI, 1.56 to 27.96; P=0.002). Panel B shows the probability of remaining free of major or minor relapse after randomization. The hazard ratio for major or minor relapse in patients in the azathioprine group, as compared with rituximab recipients, was 3.53 (95% CI, 1.49 to 8.40; P=0.01).

HR for major relapse
AZA:6.61 , Rituximab:1.56



- The RITAZAREM trial randomised relapsing patients after induction therapy with rituximab to either remaining on rituximab or switching to azathioprine for remission maintenance.
- Disease relapses were recorded in **15% (remaining**) and **38%** (**switching**) of patients over a minimum follow-up period of 36 months, and **fewer serious adverse events** were noted in the group remaining on **rituximab.**

biology

MDPI

Systematic Review

The Efficacy and Safety of Rituximab in ANCA-Associated Vasculitis: A Systematic Review

Mohammad Amin Habibi [1,2], Samira Alesaeidi [3], Mohadeseh Zahedi [1], Samin Hakimi Rahmani [1], Seyed Mohammad Piri [2] and Soheil Tavakolpour [4,*]

Table 2. *Cont.*

Author	Country	Type of Study	Number of Patients	Median Age	Sex	BVAS Score	Dose of RTX	Induction or Maintenance of RTX	Special Condition	CR or PR	Details
Brihaye et al., 2007 [64]	France	Retrospective	8 GPA	49.6	5M/3F	14.3	4 × 375 mg/m^2, 2 × 1 g	Induction	Relapsing/ refractory GPA	3 CR 3 PR 2 NR	RTX plus steroids improved clinical outcome
Durel et al., 2019 [125]	France	Retrospective	56 GPA 1 MPA 2 EGPA	46	26M/33F	9	NG	Induction	Orbital mass	64% remission with RTX vs. 26% with CYC	RTX was more effective than CYC
Timlin et al., 2015 [83]	US	Retrospective	19 GPA 12 MPA	71 ± 6	10M/21F	4.4	4 × 375 mg/m^2, 2 × 1 g	Induction	AAV patients older than 60	30/31 remission 1/31 NR	Elderly patients responded effectively to RTX
Puéchal X et al., 2019 [37]	France	Retrospective	114 GPA	52	40M/64F	9	500 mg every 6 m	Maintenance	Low-dose RTX as maintenance therapy	86% remission	Sustained remission using RTX for induction and low-dose maintenance
Azar et al., 2014 [112]	US	Retrospective	105 GPA	49	50M/55F	4	4 × 375 mg/m^2, 2 × 1 g	Induction	Evaluation of RTX with or without other maintenance therapies	95/100 CR 1/100 PR 2/100 NR 1 died 1 lost	Conventional therapies plus RTX decrease relapse rate without increasing adverse events
Charles et al., 2013 [100]	France	Retrospective	70 GPA 7 MPA 2 Renal restricted 1 EGPA	54 ± 17	NG	7	4 × 375 mg/m^2, 2 × 1 g	Both	Long-term follow-up	66% CR 25% PR	RTX was more effective as a maintenance therapy
Roll et al., 2012 [38]	Germany	Retrospective	50 GPA 8 MPA	50.2	28M/30F	NG	4 × 375 mg/m^2, 2 × 1 g	Induction	Refractory AAV	22/58 CR 29/58 PR 4/58 NR	RTX was effective in refractory AAV

* Pediatric Vasculitis Activity Score; IST: immunosuppressive therapies; RTX: rituximab; CYC: cyclophosphamide; GPA: granulomatous with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatous with polyangiitis; CR: complete remission; PR: partial remission; NR: not remission; NG: not given; NA: not assessed; F: female; M: male.

Table 3. Safety profile of RTX therapy in AAV patients.

Side Effects	Comment	Ref.
Infection	PCP, PJP, TB, UTI, salmonella, atypical mycobacterial infection, influenza, legionella, cutaneous abscess, GI infection, vulvovaginal pyoderma gangrenosome. CMV, HBV, HCV, JC virus, HSV, herpes zoster, varicella zoster, aspergillus.	[32,34,35,40,41,43,45,83,101,105,108,112,113,115,118,124,135,144,205,207,210,214,223–235]
Hypogammaglobulinemia	Hypogammaglobulinemia and severe hypogammaglobulinemia were reported in about 50% and 5% of patients. Hypogammaglobulinemia-induced infection is a controversial issue. Baseline Ig level is a substantial factor in the development of hypogammaglobulinemia.	[45,115,119,211–221]
Cancer	Breast cancer, colon, hepatocellular, hematologic, uterine, thyroid, peritoneal, renal, bladder, lung, SCC of the tongue and esophagus, basal cell carcinoma, melanoma, and non-melanoma skin cancer.	[19,32,90,91,112,124,138,236–238]
Cytopenia	Leucopenia (B-cell lymphopenia), which can be transient; thrombocytopenia; neutropenia, which can be late-onset.	[20,21,35,42,83,211,239–241]
Hypersensitivity	Hypersensitivity reaction is a first-onset complication developed in one-third of injected patients. Hypersensitivity can emerge as different symptoms such as rash and swelling.	[37,64,101,124,138]
Other side effects	CHF, AMI, VTE, bone fracture, herpes simplex osteomatitis, visual disturbance, vaginitis, pyomiosis pyoderma gangrenosome, anorexia nervosa, PML, pneumonitis, Crohn's disease, PRES, ruptured aneurysm.	[20,32,43,88,90,108,128,135,144,210,211,222,229,232,235,243–248]

- **If rituximab is contraindicated** in patients, **azathioprine remains** a **second-line approach** to remission maintenance.
- Azathioprine also plays a central role in managing ANCA-associated vasculitis during **pregnancy** because the drug is considered safe in pregnant women.
- The **REMAIN** trial compared the **continuation of azathioprine** plus glucocorticoids for **48 months** to withdrawal after **24 months**. The frequency of **overall relapses** and major disease relapses were higher in the group that received **a shorter duration** of treatment, highlighting the efficacy of extended azathioprine plus glucocorticoids for remission maintenance.

- In the MAINRITSAN2 trial, maintenance with **rituximab at fixed intervals** (**every 6 months**) was compared with tailored administration on the basis of changes in the **ANCA titre** or **reappearance of CD19+ B lymphocytes**.
- The number of infusions over the course of follow-up was reduced to three in the group treated according to the tailored regimen, compared with five in the fixed interval group.
- Although a higher percentage of patients in the tailored group had disease **flares—17% versus 10% in the fixed group—this difference was not statistically significant.**
- **Neither the ACR/VF nor the EULAR, recommendations endorse** tailored regimens of rituximab, but clinical practice varies widely.

Combination treatment with rituximab, low-dose cyclophosphamide & plasma exchange for severe ANCA-associated vasculitis

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Study Cohort

N = 64
Median Age 66

Creatinine
558 µmol/L

Dialysis-dependent
47%

Lung haemorrhage
52%

BVAS
19 (16-23)

Intervention

Plasma exchange
≥7 sessions (7-10)

Cyclophosphamide
3g total dose

Rituximab
2g total dose

Oral prednisolone
2.6g total dose

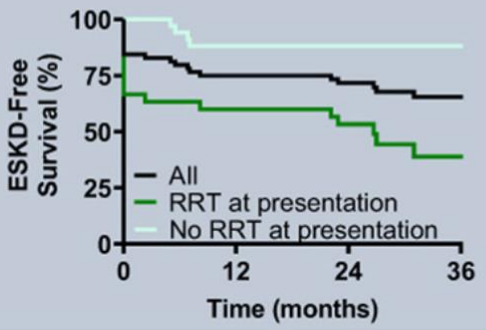
Median follow-up
46 months (26-65)

Remission & Renal Recovery

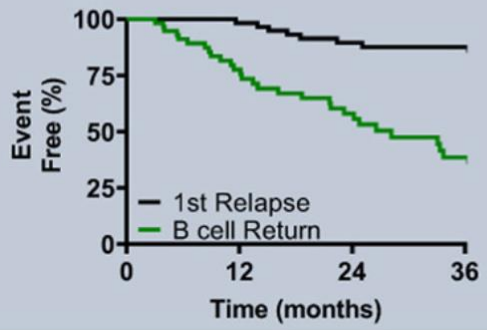
94% achieved disease remission (BVAS = 0) by 6 months
67% of patients recovered from dialysis-dependent renal failure

Long-term Outcomes

69% ESKD-free Survival: baseline kidney function predicted long-term outcome



87% Relapse-free: associated with prolonged periods of B cell depletion

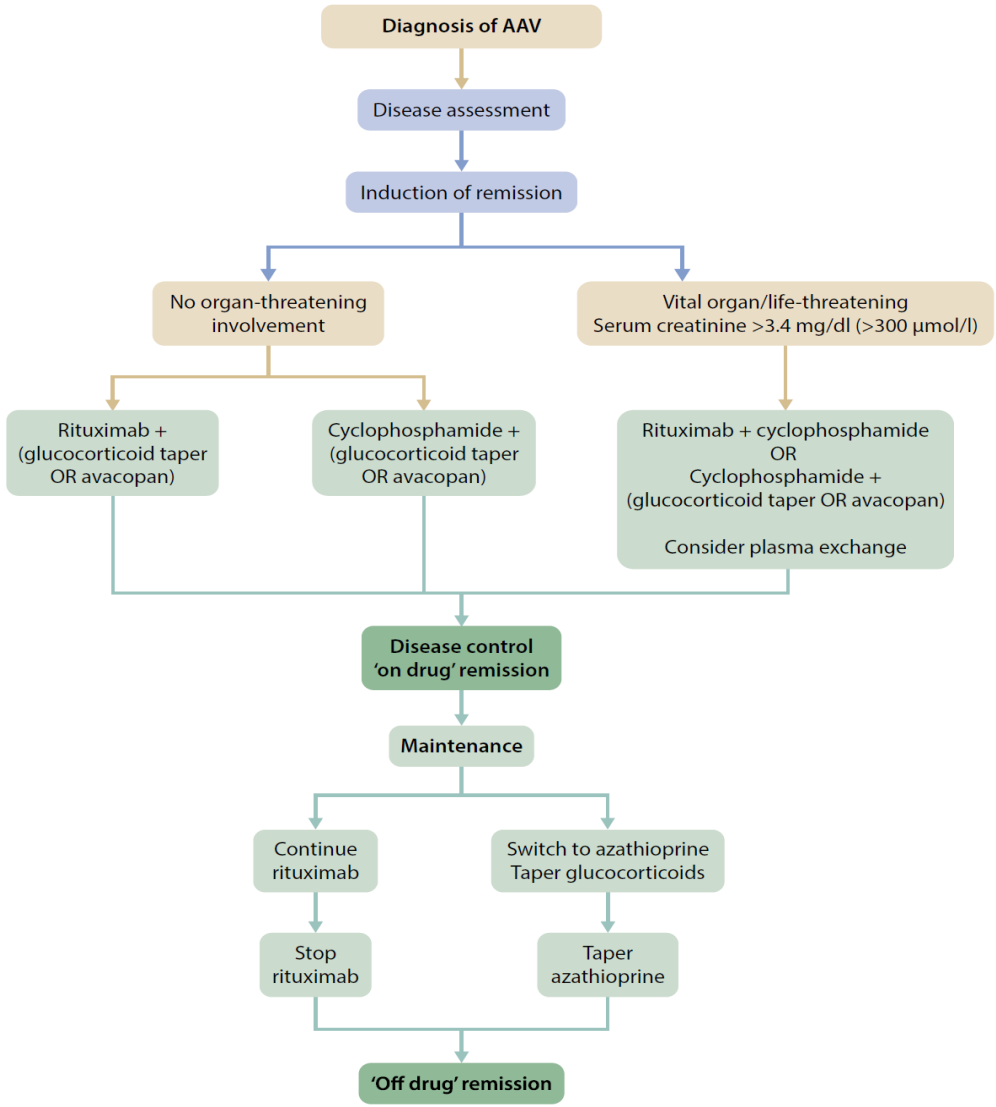


Gulati & Edwards, 2021

CONCLUSION: ***Combination immunosuppressive therapy may provide effective, prolonged disease control in patients with severe ANCA-associated vasculitis***

Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA–Associated Vasculitis

Jürgen Floege[1], David R.W. Jayne[2], Jan-Stephan F. Sanders[3], Vladimír Tesař[4], Ethan M. Balk[5], Craig E. Gordon[6], Gaelen Adam[5], Marcello A. Tonelli[7], Michael Cheung[8], Amy Earley[8] and Brad H. Rovin[9]



Challenges during remission maintenance

- **Risk of relapse**
- Several clinical parameters are known to influence the risk of relapse—eg, patients who are **PR3-ANCA positive** at baseline are more likely to relapse than those who are MPO-ANCA positive at baseline
- **ANCA negativity following remission induction**, regardless of the patient's subtype at baseline, is associated with a longer period of sustained remission compared with patients who remain ANCA positive.

- A **lower eGFR** at baseline is associated with a **lower risk of relapse**
- Nevertheless, the implications of **a renal flare in patients** with lower eGFRs at baseline are **substantially greater** than those with better preserved eGFRs because of the higher risk of subsequent end-stage kidney disease.
- For example, one study indicated that patients with a mean serum creatinine concentration of **3·9 mg/dL at baseline had a nine-fold increased risk of developing end-stage kidney disease following relapse**, compared with patients with similar levels of baseline renal dysfunction who remained in remission.

- **Specific biomarkers** indicating risk of disease relapse remain at the investigational stage and are not yet available for routine care
- However, **active glomerulonephritis** in the setting of disease relapses has been linked to an **increase in soluble CD163 in the urine**, and an assay for this marker distinguished reliably between vasculitis activity and other causes of acute kidney injury.

- Persistent haematuria at 6 months was associated with renal relapses in a study of 149 patients with ANCA-associated glomerulonephritis.
- However, another study with interval repeat kidney biopsies showed that although **60% of patients with histologically proven active disease had no haematuria**, **59% of** patients with inactive disease also had **haematuria.**

- Another study of 535 patients with kidney disease found no statistically significant predictors of renal relapse, showing that they can be difficult to diagnose.

- **C-reactive protein concentrations** and **erthyrocyte sedimentation** rates are both generally elevated during relapse, especially major ones.

- the RAVE trial showed that low baseline expression levels of **soluble immune checkpoints** (**sTim-3**, **sBTLA,** and **sCD27**) predicted the **occurrence of disease relapses** in patients with **PR3-ANCA**-associated vasculitis who were treated with rituximab.

- Hypogammaglobulinaemia is another potential concern with continuous B-cell depletion strategies.
- For patients treated with rituximab, the risk of hypogammaglobulinaemia—defined as a serum **immunoglobulin G (IgG) concentration less than 7 g/L** and associated with an **increased risk of infection**—might be **greater than 40%** 6 months after induction therapy with rituximab.

Glucocorticoid toxicity

- In the treatment of ANCA-associated vasculitis, the use of glucocorticoids has been considered unavoidable to control disease.
- the **PEXIVAS reduced-dose regimen was non-inferior to a standard-dose** regimen in terms of efficacy, substantially decreased the cumulative glucocorticoid dose needed to control the disease, and reduced the risk of serious infections.
- All three major guidelines or recommendations acknowledge the reduced-dose regimen as the new standard of care.
- The ADVOCATE trial replaced a standard prednisone taper with avacopan for ANCA-associated vasculitis and marked an important step forward for vasculitis trials, because it used a standardised instrument to measure change in glucocorticoid toxicity.

- The **avacopan group had lower Glucocorticoid Toxicity Index (GTI)** scores at both **13 weeks and 26 weeks** after treatment initiation.
- In addition, **avacopan was superior to the standard** of care in reducing glucocorticoid toxicity at several GTI thresholds, including the minimum clinically important difference of 10 points.

- Although patients who reached the primary endpoint discontinued their prednisone no later than 21 weeks into the ADVOCATE trial, **glucocorticoid toxicity continued to increase in both the avacopan group and the prednisone group** at both GTI time points.
- More than **90% of all patients in the trial had glucocorticoid toxicity at both week 13 and week 26**
- These findings underscore the need for strategies that reduce the duration of glucocorticoid courses further, minimising glucocorticoid use but still exerting and maintaining disease control.

Conclusion and outlook

- The trajectory of treatment strategies away from cytotoxic medications has been encouraging and important, but although substantial efforts have been made to reduce overall glucocorticoid burden, it remains too high.
- Novel treatment strategies over the next few years will probably include tissue-adjacent B-cell subsets with traditional anti-CD20 approaches, such as obinutuzumab or newer monoclonal antibodies targeting CD19.

- Research into anti-CD19 directed CAR-T therapies for patients with ANCA-associated vasculitis with the greatest unmet medical need is now increasing rapidly.
- Other B cell-targeted therapies aimed at immunomodulation rather than depletion, and further efforts to inhibit relevant components of complement pathways are also promising potential strategies.

- Competitive interference with the neonatal Fc receptor as a way of swiftly reducing ANCA titres to facilitate disease control is another appealing approach.
- There could also be improvement in induction and remission, with more effective and quicker means of suppressing disease flares early and approaches to remission maintenance that do not involve continuous B-cell depletion or long-term glucocorticoid use.