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Review Article

Granulomatosis with Polyangiitis (GPA) / Wegner's Granulomatosis: A Summary of Clinical Issues

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Abstract

Vasculitis can mimic many diseases; often, there are delays in diagnosis and often ends up in life/organ threatening complications without proper diagnosis and timely treatment. Patients can present with various combinations of constitutional symptoms, vasculitic symptoms, and organ involvements. ANCA tests also have many false positive and false negative results, which adds to the complexity. In addition, Anti-neutrophilic Cytoplasmic Antibody (ANCA) associated Vasculitis (AAV) have different pathological and clinical manifestations from other Vasculitis. There are four types of AAV, including Granulomatosis with Polyangiitis (GPA, previously known as Wegner's Granulomatosis), Microscopic Polyangiitis (MPA), Eosinophilic Granulomatosis with Polyangiitis (E-GPA, previously called as Churg Strauss Vasculitis), and Renal Limited / Organ limited ANCA associated Vasculitis.

This review article focuses on the elaboration of the GPA, its differentiation from other Vasculitis, including other ANCA-associated Vasculitis, its complications, and treatment options.

Keywords: Granulomatosis with Polyangiitis, Wegner's granulomatosis, ANCA associated Vasculitis, Small Vessel Vasculitis, Pauci-Immune Vasculitis.

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Introduction

Granulomatosis with Polyangiitis (formally Wegner's Granulomatosis):

Anti-neutrophilic Cytoplasmic Antibody (ANCA) associated Vasculitis (AAV) is a severe but rare multi-systemic disease. Patients can present with various combinations of constitutional symptoms, vasculitic symptoms, and organ involvements. A high index of suspicion is required for timely diagnosis and treatment of this potentially life-threatening condition.

There are four types of AAV, including Granulomatosis with Polyangiitis (GPA, previously known as Wegner's Granulomatosis), Microscopic Polyangiitis (MPA), Eosinophilic Granulomatosis with Polyangiitis (E-GPA, formerly called as Churg Strauss Vasculitis), and Renal Limited / Organ limited ANCA associated vasculitis. AAV is primarily a disease of the elderly, 60 years old and above, but can occur at any age. EGPA, on the other hand, occurs at a younger age. Pathogenesis and clinical manifestations of AAV are different from other types of Vasculitis.1.

Differences between different types of AAV

GPA is predominately idiopathic but may be due to various antigens, whereas EGPA is often an allergic response to an antigen. MPA is a variant of Poly-arteritis Nodosa (PAN). GPA commonly causes inflammatory and destructive disease affecting the eyes, upper respiratory tract, lungs, and kidneys. Necrotizing granulomas and destructive lesions affecting the airways and ear, nose, and throat (ENT) areas are more commonly seen in GPA. In contrast, they are classically absent in MPA and E-GPA. ENT involvement of EGPA is non-destructive. Asthma, eosinophilia, and non-destructive upper airways involvement with less renal involvement is common in E-GPA and helps differentiate it from GPA and MPA. On the other hand, MPA predominantly involves kidneys and lungs and usually doesn't involve ENT, eye, or upper airways. Also, there is no eosino-

philia or asthma in MPA2 [Table 1].

Diagnostic criteria of AAV

There are no well-established diagnostic criteria for the diagnosis of AAV or GPA. The American College of Rheumatology 1990 criteria for Wegener's granulomatosis classification might help establish the diagnosis. It has four criteria, sinus disease, lung involvement, renal involvement, and a biopsy showing granulomas. The presence of two or more criteria has a sensitivity of 88% and specificity of 92%. However, these criteria were developed before the routine use of ANCA and are not recommended for diagnostic purposes. The presence of ANCA supports the diagnosis, but it may be negative in up to 10% of cases.[3-5]

Positron emission tomography (PET)

FDG-PET Scan can detect inflammatory activity (increase FDG uptake) even when a routine CT scan is negative. Necrotic tissue or fibrosis will not uptake FDG. It's very sensitive for detecting ENT, airways, and thorax (including lungs, heart, and vessels) disease but is not so good for eyes and brain disease, where an MRI is more valuable. PET-CT scan also detects increased uptake of FDG in the renal cortex, indicating possible glomerulonephritis (GN).[6,7]

Anti-Neutrophilic Cytoplasmic Antibodies (ANCA)

Positive ANCA, along with the presenting features, is often diagnostic for AAV or GPA. However, ANCA can also be positive due to other causes, including infections such as hepatitis C (HCV), hepatitis B (HBV), and tuberculosis (TB). Certain drugs such as Propylthiouracil and Montelukast can also lead to positive ANCA. Other causes include cryoglobulins, anti-GBM syndrome, systemic lupus erythematosus (SLE); rheumatoid arthritis (RA); and malignancies. Indirect immunofluorescence (IIF) is used as a screening test and enzyme-linked immunosorbent assay (ELISA) for confirmation. ANCA against Proteinase-3 (PR-3), also called c-ANCA, and ANCA against Myeloperoxidase (MPO), also called p-ANCA, are specific antigens for Vasculitis. Other target antigens for ANCA are cathepsin, lysozyme, elastase, lactoferrin. ANCA doesn't use complement (unlike SLE or Cryoglobulins); hence C3, C4 is normal. That's why it is also called Pauci-Immune Vasculitis or GN (Pauci-immune means no antibodies or complement deposition is found as it is primarily a T cell-mediated injury).[2,5]

ANCA positivity: Antibody level changes are usually parallel with disease activity, relapse, and remission. Higher-level usually means severe disease. 90-95% positivity in active generalize disease, whereas ANCA is only 60% positive in limited disease. GPA & MPA have almost 90% ANCA positive results, whereas EGPA has only 40%-50% ANCA positivity. The limited renal disease has a more than 10% negative rate for ANCA. Hence, ANCA negative doesn't exclude 5-10% of AAV cases, 40% of the localized cases, or non-ANCA Vasculitis. 80% of GPAs are PR-3 specific (10% of GPA have anti-MPO, and these MPO positive GPA cases are less severe but are also less treatment responsive). Only 60% of patients have disease activity linked with ANCA titer, whereas 40% have a disease not parallel with the ANCA titer. 25-40% of limited GPAs are ANCA negative. 60% of MPA are MPO specific,

Table 1: *Mian Differentiating Feature of Various AAV*

AAV	ANCA positive	PR-3 ANCA	MPO-ANCA	Renal Involvement	Lungs	ENT, Airways & Orbit	Disease-specific
GPA	90% 60% in limited disease	80% of ANCA positive cases	10% of ANCA positive cases	75% of total cases; RPGN 50% of total cases;	Necrotizing Granulomas GGO, DPH, ILD, PAH	Destructive lesions with deformities, necrotizing lesions. Nodularity, Granulomas	Destructive ENT & airway involvement Necrotizing ill-defined granulomas. PR-3ANCA (c-ANCA).
E-GPA	40-50% Mostly with vasculitic phase	10-25 % of ANCA positive cases	75-90% of ANCA positive cases	25% of cases RPGN 15% of total cases;	Asthma Eosinophilic infiltrates GGO, DPH, ILD, PAH. DPH is less common than GPA & MPA.	Non-destructive / Non-granulomatous inflammation. Eosinophilic infiltration.	Asthma. Peripheral eosinophilia (>10%). Tissue eosinophilic infiltrates. Allergic phase, Eosinophilic phase, and Vasculitis phase. MPO-ANCA (p-ANCA)
MPA	90% of cases.	30% of ANCA positive cases	60% of ANCA positive cases	90% of all cases. RPGN 60% of total cases;	ILD, PAH, GGO, DPH.	Usually not involved	Renal involvement more than lungs MPO-ANCA (p-ANCA).

whereas 30% of MPA have PR-3 positive ANCA. As ANCAs are more positive with renal involvement, EGPA (the least renal involvement) has>50% ANCA negativity. P-ANCA and C-ANCA can overlap, and GPAs can have positive P-ANCAs.[3-5]

Biopsy and Histology

Biopsy of the affected organ (skin, kidney, lung) in a suspected case of GPA and MPA is recommended to confirm the active disease wherever possible. Skin and kidneys are the most frequently biopsied sites in GPA and MPA. Lung biopsies are rarely performed for diagnostic purposes and may be considered in unclear cases without renal or skin involvement. The presence of infections that produce granulomas (tuberculosis) should be excluded if a lung biopsy is performed to diagnose GPA or MPA. Nasal biopsies, although non-invasive, are often non-diagnostic due to the small that can be obtained from this site and are usually not considered for the diagnosis of GPA or MPA. However, a nasal biopsy may help exclude other causes such as tumors or infection.[8]

Histologically, inflammation in GPA is a mix of chronic and acute cells, including eosinophils. The granulomas seen in GPA have ill-defined margins, unlike Tuberculosis or Sarcoidosis, which have clearly defined margins of granuloma. Necrosis is geographic and is basophils due to cellular debris. The presence of the vasculitic process on biopsy is not necessary for diagnosis and is often non-specific. The presence of dense lymphocytic infiltration needs exclusion of lymphoma. ANCA subtype (Proteinase 3-ANCA in GPA, and Myeloperoxidase-ANCA in MPA and E-GPA) along with these clinical and histological features help establish the diagnosis [Table 1].[3-5,9]

Abbreviations: AAV (ANCA associated vasculitis), ANCA (Anti-Neutrophilic Cytoplasmic Antibodies), DPH (Diffuse Pulmonary Haemorrhage), E-GPA (Eosinophilic Granulomatosis with Polyangiitis), ENT (Ear, Nose, Throat), GGO (Ground glass opacities), GPA (Granulomatosis with Polyangiitis), ILD (interstitial lung disease), MPA (Microscopic Polyangiitis), MPO (Myeloperoxidase), PAH (Pulmonary Arterial Hypertension), PR-3 (Proteinase-3), RPGN (Rapidly Progressive Glomerulonephritis).

Organ Involvement in GPA:

GPA and ENT

Nodular mucosal thickening, nodules, bone and cartilage destruction, ear and mastoid infiltration/erosion by soft tissue are found in ENT areas. Otitis can also involve the 7th and 8th nerves. Destructive changes are separate from punctate erosions, and classically destruction of nasal septum and turbinate is followed by symmetrical spread to antral destruction, causing single cavity formation. Erosions look like punctuate osseous destruction on CT and are more common in the anterior ethmoid region but can involve other sinuses.[10,11]

Erosions and septal destruction are common (like lymphoma and cocaine abuse), but unlike lymphoma and cocaine abuse, the hard palate is spared in GPA. Also, soft tissue mass is only seen in lymphoma. Unlike lymphoma, there is no mass formation in GPA. Mucosal nodularity, hard palate sparing, erosion and neo-osteogenesis are common in sarcoidosis and GPA affecting sinuses, but unlike sarcoidosis, the septum is usually destroyed in GPA. Otitis and mastoiditis can be confused with infection or radionecrosis etc. Temporal bone erosion or destruction can also occur in all these. Associated abscess or sinus thrombosis goes more with infection. Bilateral ear changes should always be considered as due GPA. In GPA, sensorineural or conductive deafness, ear effusion, earache, ear discharge, facial palsy, and 8th nerve damage can all occur.[12,13]

GPA and Orbit

Orbital granuloma and inflammation, fibrosis, optic nerve damage, necrotizing scleritis, retinal Vasculitis are severe complications of GPA. Orbit (like the brain) is assessed with MRI. GPA is often lacrimal sparing (unlike sarcoidosis or lymphoma). Inflammatory or granuloma-related pseudotumor formation in the extraconal compartment is primarily unilateral, which can cause proptosis, lid edema, ophthalmoplegia, optic nerve compression, and atrophy. Later, fibrosis can result in orbital contracture (enophthalmos, optic atrophy, shrunken orbit), etc. Orbital cellulitis doesn't cause a well-defined mass, short history, and fever, which will help differentiate from GPA. Lymphoma and orbital limited sarcoidosis can cause similar presentation (pseudotumor etc.) but commonly involve the lacrimal gland (uncommon in GPA). Also, lymphoma doesn't usually cause bone erosion in orbit, unlike GPA. Cavernous haemangioma is an intraconus vascular mass that may also have calcification.[14,15]

GPA can cause ulcerative conjunctivitis ending up in conjunctival scarring, peripheral ulcerative keratitis (PUK) with risk of perforation, necrotizing scleritis with risk of thinning and perforation of the sclera and the eyeball), granulomatous uveitis (anterior, posterior or pan), choroiditis, retinal capillaritis, retinal hemorrhages, retinal vein thrombosis, ischemic optic neuritis, and atrophy. Conjunctivitis and episcleritis can be managed with topical steroids and topical immunosuppression. Everything else, including PUK and necrotizing scleritis, would also need systemic immunosuppressive therapy, including Glucocorticoids (GC), Cyclophosphamide (CYC), or Rituximab (RTX). The granuloma may not be very responsive to CYC or RTX. Refractory

granulomas with compression symptoms may need surgery, but recurrence is not uncommon.[16]

Palliative Enucleation may be necessary for severe pain syndrome if the vision is entirely and irreversibly lost. Post-operative healing issues may be there if the disease isn't well controlled. Protective glasses are helpful for those with thin sclera or cornea to reduce perforation risk by any trauma. Sclera grafting or corneal grafting may be needed too. Cataract and glaucoma are common due to ongoing inflammation or steroids use and should be operated on only when the underlying disease is well controlled.[17,18]

GPA and Airways

Airway mass can be seen in GPA, Amyloidosis, or tumors. Tracheal circumferential involvement in GPA differentiates it from pure cartilaginous pathologies (such as relapsing polychondritis or osteochondroplastic tracheobronchopathy), which spare posterior tracheal membrane. Also, tumors are not circumferential and can also have lymphadenopathy (LAP). Post intubation structure will have a history of intubation, and also (unlike GPA), no peri-stenotic mucosal edema is seen in intubation-related stricture. Amyloidosis can cause circumferential thickening. Stenosis and airway mass is common, but calcification only occurs in amyloidosis. Sarcoidosis can also cause circumferential lesions, mass, and stenosis, but LAP is not seen in GPA. Vocal cords can also be involved causing voices changes and airway obstruction. Mono-neuritis involving laryngeal nerves can also affect the larynx.[19]

GPA and Lungs

Lung nodules are often necrotizing and usually bilateral, peripheral, peribronchial, or perivascular. Ground-glass opacities (GGO), consolidations, diffuse pulmonary hemorrhages (DPH) can also be seen. LAP and tracheal thickening without lung involvement are not features of GPA (think Lymphoma, Sarcoidosis, neoplasm, infection). Pulmonary hemorrhages are more common in MPA and GPA and are not usually present in EGPA). Inflammatory lung disease (ILD) and pulmonary hypertension (PTHN) can also be seen in GPA. Granulomatous inflammation in GPA, unlike eosinophilic, infiltrates in MPA, and asthma in EGPA helps differentiate it from GPA.[20]

GPA and Nervous System

Mononeuritis multiplex or ischemic axonal polyneuropathy is more common than the central nervous system (CNS). CNS involvement usually includes meningitis, vasculitic infractions/bleeding, encephalitis, and meningitis. GPA can affect the pituitary-hypothalamus axis. Inflammatory edema or granuloma can cause expansion of pituitary stalk, pituitary gland, and hypothalamus (similar to Lymphoma, Sarcoidosis, Langerhans Cell Histiocytosis, Metastasis), leading to compression of the optic chiasma. Normal T1 hyperintensity of posterior pituitary is lost due to damage causing reduced ADH. Meningeal enhancement (patchy linear symmetrical enhancement of dura) and vasculitic brain issues (infarcts, bleed or venous thrombosis, encephalitis seen as contrast enhancement) can also be there. Granulomatous inflammation can extend to the brain from orbit or ENT. However, there can be de novo granulomatous inflammation in the brain and meninges.[21]

MRI can show contrast enhancement due to inflammation in brain parenchyma or meninges. DWI can show diffusion restrictions due to infractions (high T2 signal intensity). Progressive Multifocal Leukoencephalopathy (PML) (which can complicate immunosuppression) classically involves subcortical U fibers and doesn't have contrast enhancement or diffusion restrictions. Acute Demyelinating Encephalomyelitis (ADEM) can have similar changes as any encephalitis. GPA classically has a combination of DWI restriction (ischemia), enhancement (inflammation), and patchy high T2 signal (edema or necrosis), whereas ADEM has enhancement & high T2 signal but no restrictions. PML has a high T2 signal only but no restrictions or enhancement. U fibers are involved in both ADEM & PML. Lymphoma & sarcoidosis can cause dural masses (although GPA involves dura, masses are uncommon). Sarcoidosis affects Pia matter more (unlike GPA & Lymphoma). Infectious meningitis will have a fever and involves leptomeninges more, and CSF will help too.[22]

Skull base can be involved by GPA extension from sinuses or orbits and often affects cranial nerves (commonly olfactory and optic first, and then other nerves). Cranial nerves will be thickened and show enhancement on MRI contrast. Sarcoidosis & lymphoma can also cause similar changes. However, sarcoidosis is often bilateral, and lymphoma almost always has brain lesions. Peri-neural extension of head and neck cancers can also cause similar pictures but involves trigeminal and facial nerves more than optic and olfactory. Tumor extension also causes erosion and widening of foramina in the skull base.[23]

GPA and Renal Involvement

Out of all AAV, MPA has the most tendency to involve kidneys (90%). In contrast, renal involvement is seen in 70% of GPA cases and only 25 % in EGPA. The frequency of Rapidly Progressive Glomerulonephritis (RPGN) in MPA is higher (60%) than GPA (50%) and is least with EGPA (15%). Pauci-immune necrotizing GN, often with crescents, is the most common histological finding without immune complex deposition or

complement deposition. Patients will have glomerular haematuria, proteinuria, acute kidney injury, which can be severe enough to require dialysis, and end-stage renal disease. Tubular ischemia, atrophy, acute papillary necrosis can also be present.[1,4,5,9]

GPA, Heart, and Aorta

Aorta (abdominal more than thoracic and arch) and its branches like subclavian and carotid can also be involved due to ischemia or extension of inflammation of vasa vasorum into adjacent tissue of the main arteries. CT angiogram or MR angiogram can detect oedematous thickening, fibrosis, and narrowing. PET-CT will indicate the extent of active information. Cardiac involvement can be detected with MRI (late enhancement, LV hypokinesis, pericarditis) or PET-CT. Carditis can involve the pericardium, myocardium, conduction system, and valves.[24-27]

GPA and Gastrointestinal tract

Gastrointestinal tract (GIT) involvement is commonly mucosal ulcerations, especially ileocolitis, which can mimic inflammatory bowel disease (IBD), acute bowel ischemia, bleeding, bowel perforation, or acute surgical abdomen, which may be a disastrous complication of GPA.[28]

GPA and Skin

The skin may have ischemic ulcers, vasculitic rash, skin nodules, livedo reticularis, vasculitic urticaria, nail fold infarcts, peri-ungual infarcts, splinter hemorrhages, Raynaud's phenomena, or loss of digital tissue.[24,28]

GPA Severity & Prognostic factors:

GPA Severity

Individuals with limited or localized GPA usually present with signs and symptoms involving upper and lower respiratory tracts. They might have other features such as arthralgia, arthritis, and non-ischemic skin lesions. This group of patients is generally not considered to have life or organ-threatening disease. Typically, such patients do not have red blood casts in the urine and have a serum creatinine level of less than 1.4 mg/dL (124 μmmol/L) without evidence of a rise in creatinine above 25% of the baseline. They have a partial pressure of oxygen (PO2) above 70 mm Hg or oxygen saturation of 92% at room air and do not have evidence of other organs involvement (GIT, CNS, eyes, kidneys).[29]

On the other hand, patients with generalized or severe disease present with multisystem manifestations that may involve the lungs, kidneys, and other organs, in addition to the respiratory tract. These patients are often sicker and might require respiratory or renal support. Untreated, the disease can be fatal and life-threatening. It is unclear whether localized GPA represents an early disease that later progresses to a more severe form or is an entirely separate clinical entity. The disease is considered refractory and progressive when it does not respond to glucocorticoids and immunosuppressants such as CYC/RTX for induction or maintenance therapy.[30]

Poor prognostic factors

Age above 65 years, raised serum creatinine, advanced renal failure, and target organ involvement are poor prognostic factors. An absence of kidney involvement is associated with a 100% 5-year survival rate, compared with approximately 70% in individuals with kidney disease. Overall, the 10-year survival rate ranges from 75-88%.31 Usually, GPA has a poorer prognosis than MPA, and PR3 positive GPA has higher relapse rates than MPO positive GPA. Infection risk is higher in old age, patients on higher doses of steroids, those with neutropenia, and immunosuppression therapy.

GPA Treatment:

Induction of Remission: (A or B or C or D) [Table 2,3 &,4]

In patients with GPA or MPA who have an organ or life-threatening disease, induction therapy involving a combination of glucocorticoids with either cyclophosphamide (CYC) or Rituximab (PTX) is recommended. Plasma exchange (PEX) is also used for selected cases. The following induction regimes can be considered for initial therapy.[30-32]

A): Corticosteroids + CYC + PEX for patients presenting with;

1): Pulmonary hemorrhages

2): RPGN (Cr 4 mg/dL [354 μmol/L] or above) or dialysis requiring AKI

3): Rapidly progressive Vasculitis

4): Concomitant anti GBM positivity.

Corticosteroids: Intravenous (IV) methylprednisolone (MP) 7 -15 mg/kg (maximum 1000 mg/day) for 3 daily doses followed by oral prednisolone 1 mg/kg (maximum 60-80 mg/day) or equivalent. Prednisolone dose is gradually reduced over the next six months.

CYC: Either oral or pulse intravenous (IV) doses. Oral CYC is given daily at 1.5-2 mg/kg with appropriate dose reduction for age and renal function. IV doses are either 15 mg/kg every two weeks for three doses and then every three weeks for three to six months as employed by the CYCLOPS trial, with appropriate dose reductions made in older adults and patients with impaired kidney function. Other experts treat with 0.5 - 0.75 g/m^2 every two weeks for three to six months. No significant differences in the remission rate have been found in trials comparing daily oral and IV regimes

of CYC. IV therapy has the advantages of lower total CYC exposure and lower rates of neutropenia and infection. However, relapse rates can be higher in patients who had received IV CYC as induction therapy.

PEX: Variable dose (e.g., seven sessions over two weeks, 60 mL/kg at each session). Albumin is the preferred replacement fluid in patients with no risk of bleeding. For patients with a risk of bleeding (recent biopsy), 1-2 liters of fresh frozen plasma (FFP) can be given in place of albumin towards the end of the procedure. For patients with active bleeding, FFP can be used as replacement fluid exclusively.[30,31], [Table 2].

B): Glucocorticoids + RTX: RTX can be used in place of CYC if there is no pulmonary hemorrhage and serum creatinine is less than mg/dL (354 μmol/L). RTX is also preferred for those with previous use of CYC, risk of malignancy, or when fertility is a concern, such as the young reproductive age group. RTX Vasculitis dose is 0.375gm/m^2 infusion weekly for four weeks, or two 1 gm fortnightly doses of RTX repeated every six months (same as for rheumatoid arthritis). Antiviral for HBV, if indicated, should be continued for at least 18 months from the last dose of RTX. RTX can be used in HIV cases when CD4>50. MMF is non-inferior to CYC for non-organ threatening diseases [Table 2,4] [3-0.32].

C): Failure of either CYC or RTX to achieve remission (10% cases) usually will need a switch to the RTX or CYC (which has not been tried) or a combination of both. If even a combination of both is failing, the option is to either add MMF or IVIG. If a patient has an active infection, is pregnant, has hypogammaglobulinemia, or has a resistant disease, consider using IVIG 2gm/ kg in divided doses over 2-5 days.[30,33]

D): Azathioprine (AZP), methotrexate (MTX), or RTX with oral corticosteroids can be considered for limited and non-organ involving AAV (like ENT, arthritis, pulmonary nodules without DPH). MTX isn't used if eGFR is low or in reproductive-age females. MTX doesn't work well for renal disease.[29,30,32]

Partial remission

Remission is partial when there is a stabilization of laboratory findings and resolution of some but not all clinical abnormalities. Such cases would need additional therapeutic measures. However, the persistence of symptoms and signs or laboratory abnormalities like proteinuria, slowly worsening renal functions, etc., could also be due to irreversible chronic damage and may not mean partial or failed remission.[33]

Patients on dialysis

In patients with dialysis-dependent renal failure, the response rate to therapy is between 55-90%. Those who are not responding to induction therapy after four months have less than a 5% chance of becoming dialysis independent. Immunosuppressive treatment should be stopped in such cases unless there is an extra-renal indication. Similarly, patients with end-stage renal disease (ESRD) should be considered for immunosuppression withdrawal unless otherwise indicated. MPO has more chronic damage and higher rates of ESRD than GPA and EGPA. This is either due to the late presentation of MPA or a more kidney-focused disease. Relapse rates decrease significantly when ESRD is reached. Renal transplantation should be considered regardless of ANCA status, and graft survival is better in those who have been in remission for more than a year.[33,34]

Supportive treatment

Pneumocystis jiroveci (carinii) (PJP or PCR) Prophylaxis should be started for anyone having Prednisolone >20 mg/day for a more extended period, those on CYC, & also for other immunosuppressive drugs. Double strength trimethoprim-sulfamethoxazole (800/160 mg) given daily or three times per week, or Atovaquone 1.5gm daily (risk of hemolysis), or Dapsone 100 mg daily (risk of G6PD), or pentamidine are used. Trimethoprim-sulfamethoxazole use with MTX will increase MTX toxicity. Avoid live vaccines in patients on immunosuppressive therapy, including Prednisolone 20mg/day or more. Other vaccination, such as annual flu, pneumococcal, etc., should be given. Bone protection therapy for high-dose steroids is essential, and gastric protection may also be needed.[31,33]

Maintenance Treatment

Maintenance treatment is usually started after achieving remission with induction therapy. The timing of begi-

Table 2: *Plasma Exchange Dosing and Frequency for AAV [38]*

AAV with severe kidney disease	Vasculitis with diffuse pulmonary haemorrhage	Vasculitis in association with anti GBM
Seven treatments over a maximum of 14 days, 60ml/kg volume replacement, albumin is preferred.	Daily until bleeding stops. FFP is used as replacement.	Daily for two weeks or until anti-GBM are undetectable.

Abbreviations: AAV (ANCA-associated vasculitis), anti-GBM (anti Glomerular Basement Membrane antibodies), FFP (Fresh Frozen Plasma)

Table 3: *Summary of the Medications Used for Treating GPA*

Treatment	Induction or Maintenance	Indication	Dose / frequency	Advantages /disadvantages.
GC	Both	MP Pulse therapy Oral Prednisolone	500-1gm, infusion 3-5 days 1mg/kg/day with tapering	Rapid onset action. Multiple comorbidities
CYC	Induction mainly- Rarely maintenance for refractory disease	Severe disease Organ-threatening disease. Infusion every 4-6 months for maintenance.	500-1000mg infusion, monthly for six months. Reduce in old age and renal failure.	Gonadal toxicity, Marrow suppression Cancer risk.
RTX	Induction mainly- rarely maintenance for refractory disease	Severe disease, young age, old age, CYC is not effective or safe. 4-6 monthly infusions for maintenance	0.375gm/m2 infusion weekly for four weeks **OR** 1gm infusion at 0 & 2 weeks. Repeat six monthly.	It can be used when CYC is not safe or not tolerated. PML and decreased antibodies.
Plasma Exchange	Induction only (add on therapy to GC & CYC/RTX)	Dialysis dependent AKI RPGN with Cr>5.6. Severe refractory disease DPH. Anti GBM positive (co-existing)	Variable sessions	Clotting factor deficiency. Costly.
IVIG	Induction only (add-on therapy for refractory cases). Substitution for CYC safety issues.	Pregnancy Co-existing infection Hypogammaglobulinemia Refractory disease	2gm/kg, divided dosage in 3-5 days.	Safe in pregnancy and infections.
AZA	Maintenance mainly-rarely induction for limited disease	Maintenance (Superior to MMF & equal to MTX). Induction for localized disease.	2mg/kg/day	Safe in pregnancy. Risk of skin cancer, cytopenia, and hepatotoxic.
MMF	Maintenance mainly-rarely induction for limited disease	Second-line maintenance option. It can be added for induction in refractory cases.	2-3gm/day	Not as effective as AZA for maintenance. Not safe in pregnancy.
MTX	Maintenance mainly-rarely induction for limited disease	Second-line maintenance if AZA is not tolerated. Second-line option for induction for localized disease.	10-25mg/weekly	It can't be used in renal disease. Not effective for renal issues. Caution with Bactrim use. Teratogenic.

Abbreviations: AKI (Acute Kidney Injury), AZA (Azathioprine), Cr (Creatinine), CYC (Cyclophosphamide), GC (Glucocorticoids), gm (gram), GPA (Granulomatosis with Polyangiitis), IVIG (Intravenous Immunoglobulins), mg (milligram), MMF (Mycophenolate), MP (Methylprednisolone), MTX (Methotrexate), PML (Progressive Multifocal Leukoencephalopathy), RPGN (Rapidly Progressive Glomerulonephritis), RTX (Rituximab).

nning maintenance therapy depends on the induction regime used. Maintenance treatment is started 2-4 weeks following CYC or after 4-6 months following the last dose of RTX. Maintenance therapy should be continued for a minimum of 18 months at least or 24 months for PR3 (GPA) which has a higher relapse. It may need to continue for a more extended period or even indefinite for those with persistent disease or frequent relapses.

RTX, AZP, MMF, and MTX have all been used for maintenance therapy. Choice of agents depends on the patient-specific factors, institutional guidelines, and physician familiarity and experience in using a particular agent. Refractory disease or the ones with difficult remission; can use RTX 0.5-1gm every 4-6 months or CYC 1 gm infusion every 4-6 months. RTX is preferred over AZP. In order of effectiveness for remission; RTX > AZA > MMF (AZA=MTX) [Table 2]. AZP 2mg/kg/day for maintenance is superior to MMF 1gm BD (unlike Lupus, where MMF is better). For those with risk of cancer, ineffective AZP, or AZP intolerance, MMF is used as the second line. MTX 20-

25 mg/week can also be used, but it's less protective for kidneys. Also, MTX can't be used in CKD cases. Calcineurin inhibitors (CNI) such as tacrolimus or cyclosporine can be used as second-line if myelosuppression is a problem. Avacopan (C5 inhibitor) can replace steroids in the induction regimen with CYC or RTX.[30-33]

Table 4: *Reduced Dose of Oral Prednisolone for ANCA-Vasculitis*[38]

Week	Weight <50kg	Weight 50-70kg	Weight ?75kg
1	50mg	60mg	75mg
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	55	5
21-22	5	5	5
23-52	5	5	5
>52	Local practice	Local practice	Local practice

GPA Relapse & Monitoring:

Relapse

Mild relapse can be managed by increasing oral medications, e.g., increasing steroids to the dose that was being used when remission was achieved. It can be continued for four weeks and then slowly tapered to a low dose. There may be a need for changing the maintenance drugs for recurrent relapses. Severe relapse will need reintroduction of induction therapy. The relapse rate is higher among patients with Staphylococcus Aureus nasal carriage. (Bactrim is used prophylactically). Old age, renal disease, pulmonary hemorrhages, female sex, ongoing infection, ANCA level, T-cell activation level, a genetic tendency are also high relapse risks. 30% of patients relapse in 2 years and 50% in 5 years (same for AZP and MTX). 17% of cases of renal transplantation can have a recurrence while being on CNI.[35]

ANCA level rises in those who have remained ANCA positive after achieving remission or becomes positive again in patients having a relapse. However, rising ANCA titer alone in the absence of other features suggestive of relapse doesn't need titration on immunosuppression but requires more close monitoring. Moreover, relapse can happen without a rise in ANCA titer or even with falling ANCA titer. Non-renal relapse may not have any increase in ANCA.[34,35]

Long term monitoring

Monitoring for drug toxicities such as CYC-related transitional cell carcinoma (TCC) of the bladder, AZP related skin cancers, and RTX-related PML (if this happens, reduce immunosuppressive medications and treat the AAV with steroids). In addition, monitoring for blood counts and renal and liver functions is essential for these drug-related side effects. Disease-related monitoring includes monitoring for disease symptoms and signs, routine lab parameters such as urine tests for proteinuria and microhematuria, renal functions, inflammatory markers, and ANCA level.[30-37]

Discussion & Conclusion

Vasculitis can have many different presentations, delayed diagnosis, complex investigations, organ/life threatening complications, and treatment depends on severity and patient's comorbidities. Often, induction therapy followed by maintenance treatment is needed wit use of glucocorticoids and immunosuppressive therapies. Every effort should be made to minimize the disease and treatment related complications. Treatment should be under care of multiple subspecialities depending on the extent of the disease such as rheumatology & nephrology. Patient education and involvement in decision making is essential.

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