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Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis)

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ABSTRACT

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's Granulomatosis) is an autoimmune small vessel vasculitis which is highly associated with anti-neutrophil cytoplasmic antibodies (ANCA). The hallmarks of this condition are systemic necrotising vasculitis, necrotising granulomatous inflammation, and necrotising glomerulonephritis. The aetiology of granulomatosis with polyangiitis is linked to environmental and infectious triggers inciting onset of disease in genetically predisposed individuals. Anti-neutrophil cytoplasmic antibodies are pathogenic and play an important role in the pathogenesis of this disease, although ANCA positivity is not essential for a clinical diagnosis of granulomatosis with polyangiitis. Granulomatosis with polyangiitis is diagnosed based on clinical manifestations of systemic vasculitis and histological evidence of necrotising vasculitis or granulomatous inflammation. This small vessel vasculitis may present as limited disease of the ears, nose and upper airways or mild, moderate or severe systemic disease. Immunosuppression and adjuvant therapies have contributed to the improved prognosis of granulomatosis with polyangiitis over the past decades. Treatment strategies are tailored to the severity of the disease. They are based on published evidence of the efficacy and safety of the immunosuppressive drugs indicated to manage active vasculitis and maintain clinical remission. This review will summarise the history, aetiology, pathogenesis, classification, diagnosis and management of granulomatosis with polyangiitis.

1. Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's Granulomatosis) is an autoimmune small vessel vasculitis which is highly associated with anti-neutrophil cytoplasmic antibodies (ANCA) and has clinical manifestations which include systemic necrotising vasculitis, necrotising granulomatous inflammation, and necrotising glomerulonephritis. It was first described in the medical literature in a clinical case report in the late 19th century and was formerly known by the eponymous name, Wegener's Granulomatosis, after Friedrich Wegener who described the clinical triad associated with this disease in 1936. The use of disease-descriptive, aetiology based nomenclature is now recommended and preferable to the use of eponymous names, therefore since 2011 Wegener's Granulomatosis has been known as granulomatosis with polyangiitis (abbreviated to GPA). This was recommended by the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and American Society of Nephrology (ASN) and is the name which should be used in clinical practice and medical literature for the ANCA-associated vasculitis, formerly known as Wegener's Granulomatosis [1].

2. Epidemiology

The annual incidence of GPA is 5–10 cases per million population with equal frequency in males and females [2]. GPA is very rare in childhood and young adults. The reported peak incidence of GPA is in the 7th decade of life between the ages of 65 and 70 years [3]. The published point prevalence of GPA ranges between 24 and 157 cases per million with a distinctly higher prevalence of GPA amongst Caucasians, especially those from Northern Europe, compared to Asian, African, Afro-Caribbean and African-American populations [2–4].

3. Aetiology

The aetiology of GPA may originate from infectious, environmental, chemical, toxic or pharmacological triggers in people who are genetically predisposed to this autoimmune disease [2].

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3.1. Infectious triggers

Infectious triggers include bacterial, mycobacterial, fungal or viral infections of the ears, nose and respiratory tract. *Staphylococcus aureus* nasal carriage is a common trigger of GPA flares.

3.2. Environmental triggers

Environmental triggers which may contribute to the onset of GPA are pollution, smoking, inhaled toxins, inhaled chemicals and exposure to metals, such as mercury or lead [4].

3.3. Drug-induced ANCA-associated vasculitis

Drug induced ANCA-associated vasculitis differs from primary ANCA-associated vasculitis and coincides with the initiation of a drug. It usually subsides with discontinuation of the offending drug, however in genetically predisposed people it may be the inciting event to the onset of GPA. Examples of drugs known to trigger drug-induced ANCA-vasculitis are antibiotics: cefotaxime, minocycline; anti-thyroid medication: benzylthiouracil, carbimazole, methimazole, prophythiouracil; anti-tumour necrosis factor alpha agents: adalimumab, etanercept, infliximab; psychoactive drugs: clozapine, thioridazine; other drugs: allopurinol, cocaine, D-penicillamine, hydralazine, levamisole, phenytoin and sulfasalazine [5].

3.4. Genetics

Genetic predisposition to ANCA associated vasculitis has been studied and familial association studies report a 1.56 increased relative risk of developing GPA in people who have a first degree relative with GPA [4].

There is an increased susceptibility to proteinase-3 ANCA associated vasculitis with certain genetic variants. MHC class II HLA-DP1*0401 has a strong association with PR3-AAV GPA; MHC class II HLA-DRB1*15 genotype in African-Americans is associated with a 36× increased risk of PR3-AAV and MHC class II HLADRB*1501 allele in Caucasians is associated with a 73× increased risk of PR3-AAV [4]. Single nucleotide polymorphisms (SNPs) in certain genes may predispose to GPA. A SNP in *SERPINA1*, a gene which encodes for α_1-antitrypsin, which is a neutral serine protease inhibitor of the proteinase 3 enzyme, is linked to GPA and a SNP in *PRTN3*, a gene which encodes proteinase 3 is also associated with GPA [4]. *CTLA-4* gene polymorphism is linked to the development of GPA because the action of T lymphocytes is inhibited due to defective binding of CTLA-4, expressed mainly on CD4+ T lymphocytes, to CD80 and CD86 on antigen presenting cells (APCs) [4,6].

4. Pathogenesis

The immunopathogenesis of GPA is complex and involves the generation of ANCA against proteinase 3 (PR3) in approximately 80% of GPA patients and against myeloperoxidase (MPO) in approximately 10% of GPA patients [4]. Antibodies against lysosome associated membrane protein-2 (LAMP-2) may also play a role in the pathogenesis of GPA via a process of molecular mimicry [4].

At present, the immunopathogenesis of GPA is thought to stem from environmental or infectious triggers in a genetically predisposed individual who lacks tolerance to ANCA self-antigens. The noxious triggers lead to an inflammatory response with secretion of pro-inflammatory cytokines and ANCA production in genetically predisposed individuals. *Staphylococcus aureus* is a common micro-organism implicated in the pathogenesis of GPA and the recurring, relapsing nature of the disease may be linked to persistent colonisation of nasal passages with this organism. *Staphylococcus aureus* produces super-antigens which activate B and T cells, and via a process of molecular mimicry *Staphylococcus aureus* can also induce AAV [4].

Patients with GPA generally have elevated B lymphocyte stimulator factors, such as B cell activation factor (BAFF) and a relative abundance of T follicular helper cells (TFH) compared to healthy individuals [7,8]. This could explain the increased frequency of self-reactive B lymphocytes in GPA patients. These self-reactive B lymphocytes may mature into long-lived plasma cells which secrete ANCA, the pathogenic antibody associated with GPA, which binds to proteinase 3 on neutrophil and monocyte surfaces. In the presence of ANCA, neutrophils and monocytes generate and release reactive oxygen species, proteases, cytokines and neutrophil extracellular trap products (NET-derived products) are generated [4]. Dendritic cells can be activated by NET-derived products through toll-like receptors (TLR) and the release of interferon-alpha (IFN-α) impairs T regulatory cell function [4]. Activation of the alternative complement pathway, results in the formation of the membrane attack complex (C5b6789 MAC) which promotes ANCA associated neutrophil activation, inflammation and tissue damage [4].

These pro-inflammatory pathways lead to the development of necrotising systemic vasculitis, necrotising glomerulonephritis and granulomatous inflammation predominantly of the airways, which are hallmarks of GPA.

5. Clinical manifestations of GPA

Patients with clinically active granulomatosis with polyangiitis may present with constitutional symptoms of disease such as general malaise, myalgia, arthralgia, anorexia, weight loss and pyrexia.

Cutaneous signs such as leucocytoclastic vasculitis, digital infarcts, purpura, cutaneous ulcers and gangrene occur in GPA, however they are non-specific manifestations of systemic vasculitis which contribute to a clinical diagnosis of GPA and are not pathognomonic [9].

Mucocutaneous and orbital manifestations of active GPA include oral ulcers, oral granulomatous lesions, episcleritis, scleritis, conjunctivitis, keratitis, uveitis, retinal vasculitis, retinal arterial or venous thrombosis, retinal exudates, retinal haemorrhages, blurred vision, blindness, proptosis and orbital granulomatous masses [10].

Ear, nose and upper airway clinical manifestations are common amongst GPA patients. Sensorineural hearing loss and conductive hearing loss result in auditory morbidity. Nasal signs of active GPA include persistent, recurrent nasal discharges, blood-stained nasal discharge, epistaxis, nasal crusting, nasal ulceration, nasal bridge collapse, nasal granulomatous lesions, parasinus and sinus inflammation, with associated regional tenderness [11]. Upper airway obstructive disease occurs in the form of subglottic or tracheal stenosis [11]. Lower respiratory tract manifestations of active GPA include cough, breathlessness, stridor, wheeze, small airway obstruction, pulmonary nodules, cavitating lung lesions, pleuritis, pleural effusions, pulmonary infiltrates, pulmonary haemorrhage, due to alveolar capillaritis and respiratory failure [12].

Cardiovascular GPA clinically presents as small vessel vasculitis, occlusive vascular disease, pericarditis, pericardial effusions, cardiomyopathy, valvular heart disease, ischaemic hear disease and heart failure [11].

Gastrointestinal GPA manifests as an acute abdomen secondary to peritonitis or bowel ischaemia which may be secondary to mesenteric vasculitis [13].

Renal GPA is a diffuse pauci-immune crescentic necrotising glomerulonephritis which can be clinically suspected if the patient has haematuria, proteinuria, cellular casts on urine cytology, and

renal impairment manifested as acute kidney injury, chronic kidney disease or end-stage renal failure [11].

Central nervous system (CNS) and peripheral nervous system (PNS) GPA has a variety of clinical presentations which include headache, meningitis, seizures, cerebrovascular accidents, spinal cord lesions, cranial nerve palsies, sensory or motor peripheral neuropathy, mononeuritis multiplex; sensorineural hearing loss and cerebral mass lesions [14]. Musculoskeletal (MSK) manifestations of GPA include inflammatory arthritis, which is rarely erosive or deforming, arthralgia and myalgia.

6. Classification criteria for GPA

The American College of Rheumatology Classification Criteria for GPA are useful criteria that have been used since inception to classify GPA as a separate disease from other forms of systemic vasculitis and to facilitate clinical research with a standardised group of patients. The criteria have limitations because they may not distinguish GPA from microscopic polyangiitis (MPA) and vasculitis mimics (Table 1).

7. Diagnosis of GPA

There are no diagnostic criteria for GPA and diagnosis is based on a combination of the clinical manifestations of systemic disease which suggest a diagnosis of vasculitis; positive ANCA serology and histological evidence of necrotising vasculitis, necrotising glomerulonephritis or granulomatous inflammation from a relevant organ biopsy, such as the skin, lung or kidney. The severity of AAV can be assessed using a disease activity instrument such as the Birmingham Vasculitis Activity Score (BVAS) which can categorise GPA as mild, moderate, severe or life-threatening depending on the extent of the organ involvement [15].

The prompt diagnosis of GPA patients is important for prognostic reasons, as there are effective immunosuppression regimes that can induce clinical remission and in the long-term reduce disease morbidity and mortality.

It should be emphasised that positive ANCA serology is not essential for the diagnosis of GPA if the clinical and histological findings point to a diagnosis of GPA, and that relevant steps should be taken to exclude vasculitis mimics or other types of systemic vasculitis. Caution should also be taken in interpreting positive ANCA serology in patients who do not exhibit an array of clinical signs or symptoms suggestive of AAV or who do not have histological evidence of a systemic vasculitis.

ANCA immunofluorescence (IF) qualitative assays identify cytoplasmic c-ANCA, perinuclear p-ANCA and atypical ANCA. Enzyme immunosorbent assays (ELISA) are quantitative and measure PR3-ANCA and MPO-ANCA titres. The use of IF and ELISA in ANCA testing gives a 96% sensitivity and 98.5% specificity for AAV, with 88% GPA patients being seropositive for c-ANCA (Table 2).

Table 1
ACR classification criteria for granulomatosis with polyangiitis (formerly, Wegener's Granulomatosis).

	Classification criteria	
1.	Nasal or Oral inflammation	Painful or painless oral ulcers or purulent or bloody nasal discharge.
2.	Abnormal chest radiograph	Pulmonary nodules, fixed pulmonary infiltrates or pulmonary cavities.
3.	Abnormal urinary sediment	Microscopic haematuria with or without red cell casts.
4.	Granulomatous inflammation	Biopsy of an artery or perivascular area shows granulomatous inflammation.

The presence of two or more of these four criteria yields a sensitivity of 88 percent.
The presence of two or more of these four criteria yields a specificity of 92 percent.

Table 2
Investigations for the diagnosis of granulomatosis with polyangiitis.

Test	Indication and clinical relevance in the diagnosis of GPA
Blood tests	
Full blood count	Anaemia, leucocytosis, eosinophilia (eGPA)
Urea electrolytes creatinine	Acute kidney injury, chronic kidney disease and ESRF
Liver function tests	Hypoalbuminemia, hepatitis
Bone profile + ACE	Sarcoidosis
ESR/CRP	Elevation of ESR and CRP in active vasculitis
Immunology	ANCA-IF and ELISA c-ANCA or pANCA PR3 MPO titres in AAV ANA +/− ENA (SLE or other autoimmune disease associated vasculitis) RhF (Rheumatoid vasculitis) Anti-GBM (Goodpasture's disease pulmonary-renal haemorrhage) Cryoglobulins (cryoglobulinaemia) Immunoglobulins (hypergammaglobulinaemia)
Infection screen	
Blood cultures	Sepsis (vasculitis mimic)
Sputum cultures	Tuberculosis, bacterial infections (vasculitis mimic)
Viral serology	Viral serology (HIV, HBV, HCV related vasculitis)
Urine analysis	
Urine dipstick	Haematuria, proteinuria (renal vasculitis) leucocytes and nitrites (infections)
Urine cytology	RBC casts, microscopic haematuria (renal vasculitis)
Urine protein	Urine proteinuria (renal vasculitis or nephritic syndrome)
Radiographs	
Chest radiograph	Lung nodules, lymphadenopathy, lung infiltrates, lung cavities, pulmonary haemorrhage, consolidation, pleural effusions
CT chest	Atelectasis, consolidation, lung masses, laryngeal stenosis, tracheo-bronchial stenosis, bronchiectasis, pleural thickening, pleural effusions and lymph nodes
HRCT chest	Patchy or diffuse ground-glass opacification, alveolar haemorrhage
Sinus CT	Sinus opacification, mucosal thickening and bone destruction
Brain and orbits MRI	Granulomatous lesions, pachymeningitis, orbital nerve compression, cerebral vasculitis
Lung function tests	Spirometry (restrictive or obstructive airways), DLCO (pulmonary haemorrhage)
Bronchoscopy	Transbronchial biopsy and bronchial washings/lavage
EMG/NCS	Peripheral sensorimotor neuropathy, myositis
Biopsy	
Skin	Leucocytoclastic vasculitis (commonest), cutaneous vasculitis
Masses	Granulomatous lesions
Lung	Pulmonary vasculitis, granulomatous and non-granulomatous lesions, respiratory tract tissue vasculitis
Renal	Segmental, necrotising, crescentic pauci-immune glomerulonephritis
Peripheral nerve	Sensorimotor polyneuropathy, mononeuritis multiplex
Muscle	Myositis (vasculitis mimics)

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody associated vasculitis; ACE, angiotensin converting enzyme; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CT, computed tomography scan; CRP, C-reactive protein; DLCO, diffusing lung capacity for carbon monoxide; eGPA, eosinophilic granulomatosis with polyangiitis; ELISA, enzyme linked immunosorbent assay; EMG, electromyelogram; ENA, anti-extractable nuclear antigen antibodies; ESR, erythrocyte sedimentation rate; ESR, end-stage renal failure; GN, glomerulonephritis; anti-GBM, anti-glomerular basement membrane antibody; GPA, granulomatosis with polyangiitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRCT, high resolution CT scan; IF, immunofluorescence; MPO, myeloperoxidase; MRI, magnetic resonance imaging; NCS, nerve conduction studies; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; PR3, proteinase 3; RhF, rheumatoid factor antibodies; SLE, systemic lupus erythematosus.

8. Management of GPA

GPA is an autoimmune systemic small vessel ANCA associated vasculitis which requires prompt, effective management of the

acute and chronic manifestations of disease. Once the diagnosis of GPA has been established, clinicians should devise an appropriate treatment strategy for each individual patient, based on current clinical evidence, treatment guidelines and recommendations.

Consideration should be given to the potential benefits, side-effects and risks of all treatment options discussed with patients, in order to provide the patients with a management plan that is most likely to induce disease remission, maintain disease remission and have the least toxicity possible.

8.1. Induction therapy in GPA

8.1.1. Cyclophosphamide

Cyclophosphamide and corticosteroid combination therapy has been used since the 1970s for the management of AAV. Oral cyclophosphamide and pulsed intravenous cyclophosphamide are equally effective in remission induction in AAV [16,17]. The toxicity of cyclophosphamide necessitates a limitation in the duration of treatment in order to minimise the risk of severe immunosuppression, opportunistic infections, bone marrow suppression, haemorrhagic cystitis, bladder cancer, risk of malignancies and infertility [17]. Mesna, a drug that binds the toxic metabolite of cyclophosphamide, acrolein, is co-administered with cyclophosphamide to minimise the incidence of haemorrhagic cystitis [17]. Regular monitoring of full blood count, renal function, liver function, urine cytology and clinical symptoms is recommended for patients treated with cyclophosphamide. In addition, patients should be counselled prior to treatment with cyclophosphamide about the potential side-effects, fertility risks of cyclophosphamide and the teratogenicity of cyclophosphamide.

8.1.2. Rituximab

Rituximab is an anti-CD20 IgG1 chimeric, monoclonal antibody B cell depletion biologic therapy, which was approved by the United States Food and Drug Administration (FDA) in 2011 for the management of GPA and MPA ANCA associated vasculitis. It is approved for induction of disease remission and management of severe, relapsing GPA at a dose of 375 mg/m^2 weekly for 4 weeks.

The RAVE (Rituximab in Anti-neutrophil Cytoplasmic Antibody-Associated Vasculitis) trial demonstrated the non-inferiority of rituximab to cyclophosphamide in remission induction and further interpretation of the results suggests superiority of rituximab in relapsing GPA. There are no significant differences in adverse events reported in the rituximab treated patients compared to cyclophosphamide in the clinical trial [18].

The European Vasculitis Study Group (EUVAS) RITUXVAS trial of rituximab for GPA with renal vasculitis showed that rituximab is effective but not superior to cyclophosphamide in inducing GPA remission. It did not show a difference in adverse event reporting between rituximab and cyclophosphamide [19].

Rituximab has greater efficacy in the vasculitic phase compared to the granulomatous phase of GPA [20].

Important potential adverse events associated with rituximab treatment include severe immunosuppression after B cell depletion, progressive multi-focal leucoencephalopathy associated with reactivation of JC virus, hypogammaglobulinaemia, opportunistic infections, malignancy, allergic or anaphylactic reactions and infusion reactions.

8.1.3. Methotrexate

Limited or mild non-organ, non-life threatening GPA may be treated with Methotrexate for remission induction at an average dose of Methotrexate 15–25 mg/week and folic acid is co prescribed [21]. However, methotrexate induction may be associated with a higher relapse rate in comparison to patients treated with a cyclophosphamide containing induction regimen [22].

8.1.4. Glucocorticosteroids

Glucocorticosteroids are prescribed in conjunction with induction therapy immunosuppressants and are not prescribed as monotherapy to induce clinical remission in GPA. Methylprednisolone 500–1000 mg intravenously daily for 3 days is followed by oral prednisolone 0.5–1 mg/kg/d for at least 4 weeks. Corticosteroids are prescribed at high doses whilst the disease is active then gradually tapered to the lowest dose of corticosteroid required to maintain remission with concomitant immunosuppressive drugs. However, given that high doses of corticosteroids can be associated with early accumulation of damage, there is a consensus that much lower doses should be considered whenever this is possible.

8.2. Maintenance therapy in GPA

Maintenance therapy is important in reducing the incidence of GPA relapse, organ failure and life-threatening disease and is initiated after completion of induction therapy for a minimum of 12–18 months.

8.2.1. Azathioprine

An immunosuppressant recommended for GPA maintenance therapy is azathioprine 2 mg/kg/day, which has evidence from the CYCAZAREM study (Cyclophosphamide Versus Azathioprine During Remission in ANCA-Associated Vasculitis) [23]. The CYCAZAREM trial data shows that azathioprine is safer than oral cyclophosphamide and is as effective in maintaining clinical remission in AAV [23]. The WEGENT trial data reported that azathioprine is as effective as methotrexate for maintenance therapy in GPA. Azathioprine and methotrexate have similar safety profiles and relapse rates, however azathioprine has an advantage over methotrexate, since it can be prescribed in pregnancy but methotrexate is contraindicated in pregnancy. The IMPROVE trial reported the superiority of azathioprine to mycophenolate mofetil in maintenance therapy in GPA [24].

8.2.2. Methotrexate

Methotrexate is an effective maintenance therapy for mild or limited GPA. After cyclophosphamide induction therapy the effectiveness of methotrexate improves [25,26].

8.2.3. Leflunomide

Leflunomide 20–30 mg/day is more effective in reducing relapse rates in GPA than methotrexate. However it is associated with numerous adverse effects including severe hypertension, severe bone marrow suppression and immunosuppression [27].

8.2.4. Rituximab

In the future it may become apparent what role rituximab may play in maintenance of disease remission in GPA. To date, published data from a fixed interval rituximab retreatment protocol of rituximab iv 1 g 6 monthly for 2 years after remission induction therapy, reports a reduction in the relapse rate and prolongation of the remission period in GPA patients [28].

8.3. Adjuvant therapy

Cotrimoxazole (trimethoprim/sulfamethoxazole 800 mg/160 mg) 3 times per week prophylaxis is an adjuvant therapy which may reduce relapse rate and aid in the maintenance of clinical remission [29]. Caution is advised to avoid co-prescribing cotrimoxazole in patients also on weekly methotrexate therapy on account of the risk

of bone marrow suppression. Alternative antibiotics may be prescribed in patients who are allergic to sulphur.

8.4. Plasma exchange

Plasma exchange (PEX) is proposed to work by eliminating ANCA from the peripheral circulation. PEX in conjunction with cyclophosphamide can be used in patients with rapidly progressive life-threatening renal vasculitis, as it may prolong dialysis free survival [30,31]. In severe AAV alveolar haemorrhage, PEX may be prescribed with appropriate immunosuppressant drugs, particularly if anti-glomerular basement membrane antibodies are also detected [32].

9. Final comments

The management of granulomatosis with polyangiitis continues to develop and trial data from the belimumab remission in vasculitis trial of the efficacy and safety of combination azathioprine and belimumab therapy after standard induction therapy in ANCA associated vasculitis, is a future prospect. Finally, we note recent reviews that highlight some basic biologic aspects, including therapy, not covered herein [33–38].

Conflict of interest

Authors have no conflicts of interest.

References

[1] Falk RJ, Gross WL, Guillevin L, Hoffman G, Jayne DR, Jennette JC, et al. Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis. Ann Rheum Dis 2011;70(4):704.
[2] Scott DG, Watts RA. Systemic vasculitis: epidemiology, classification and environmental factors. Ann Rheum Dis 2000;59(3):161–3.
[3] Lane SE, Watts R, Scott DG. Epidemiology of systemic vasculitis. Curr Rheumatol Rep 2005;7(4):270–5.
[4] Cartin-Ceba R, Peikert T, Specks U. Pathogenesis of ANCA-associated vasculitis. Curr Rheumatol Rep 2012;14(6):481–93.
[5] Gao Y, Zhao MH. Review article: drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Nephrol (Carlton) 2009;14(1):33–41.
[6] Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367(3):214–23.
[7] Zhao Y, Odell E, Choong LM, Barone F, Fields P, Wilkins B, et al. Granulomatosis with polyangiitis involves sustained mucosal inflammation that is rich in B-cell survival factors and autoantigen. Rheumatol (Oxford) 2012;51(9):1580–6.
[8] Abdulahad WH, Lepse N, Stegeman CA, Huitema MG, Doornsbos-van der Meer B, Tadema H, et al. Increased frequency of circulating IL-21 producing Th-cells in patients with granulomatosis with polyangiitis. Arthritis Res Ther 2013;15(3):R70.
[9] Daoud MS, Gibson LE, DeRemee RA, Specks U, el-Azhary RA, Su WP. Cutaneous Wegener's granulomatosis: clinical, histopathologic, and immunopathologic features of thirty patients. J Am Acad Dermatol 1994;31(4):605–12.
[10] Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. Surv Ophthalmol 2010;55(5):429–44.
[11] Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med 2004;117(1):39–50.
[12] Gomez-Puerta JA, Hernandez-Rodriguez J, Lopez-Soto A, Bosch X. Antineutrophil cytoplasmic antibody-associated vasculitides and respiratory disease. Chest 2009;136(4):1101–11.
[13] Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. Med (Baltimore) 2005;84(2):115–28.
[14] Holle JU, Gross WL. Neurological involvement in Wegener's granulomatosis. Curr Opin Rheumatol 2011;23(1):7–11.
[15] Mahr AD, Neogi T, Lavalley MP, Davis JC, Hoffman GS, McCune WJ, et al. Assessment of the item selection and weighting in the Birmingham vasculitis activity score for Wegener's granulomatosis. Arthritis Rheum 2008;59(6):884–91.
[16] Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68(3):310–7.
[17] de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in anti-neutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150(10):670–80.
[18] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363(3):221–32.
[19] Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363(3):211–20.
[20] Aries PM, Hellmich B, Voswinkel J, Both M, Nolle B, Holl-Ulrich K, et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006;65(7):853–8.
[21] De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52(8):2461–9.
[22] Faurschou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Hoglund P, et al. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64(10):3472–7.
[23] Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert J, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349(1):36–44.
[24] Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. J Am Med Assoc 2010;304(21):2381–8.
[25] Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. Am J Med 2003;114(6):463–9.
[26] Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum 1999;42(12):2666–73.
[27] Metzler C, Miehle N, Manger K, Iking-Konert C, de Groot K, Hellmich B, et al. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. Rheumatol (Oxford) 2007;46(7):1087–91.
[28] Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64(11):3760–9.
[29] Kallenberg CG. Treatment of Wegener's granulomatosis: new horizons? Clin Exp Rheumatol 1996;14(1):1–4.
[30] Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int 1991;40(4):757–63.
[31] Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18(7):2180–8.
[32] Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis 2003;42(6):1149–53.
[33] Sangle SR, Lutalo PM, Davies RJ, Khamashta MA, D'Cruz DP. B-cell depletion therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. J Autoimmun 2013;43:55–9.
[34] Thurner L, Preuss KD, Fadle N, Regitz E, Klemm P, Zaks M, et al. Progranulin antibodies in autoimmune diseases. J Autoimmun 2013;42:29–38.
[35] Noel N, Andre C, Bengoufa D, Dehoulle C, Mahler M, Limal N, et al. Performance evaluation of three assays for the detection of PR3-ANCA in granulomatosis with polyangiitis in daily practice. Autoimmun Rev 2013;12:1118–22.
[36] Pugnet G, Pagnoux C, Bezanahary H, Ly KH, Vidal E, Guillevin L. Progressive multifocal encephalopathy after cyclophosphamide in granulomatosis with polyangiitis (Wegener) patients: case report and review of literature. Clin Exp Rheumatol 2013;31(1 Suppl. 75):S62–4.
[37] Millet A, Pederzoli-Ribeil M, Guillevin L, Witko-Sarsat V, Mouthon L. Anti-neutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group. Ann Rheum Dis 2013;72:1273–9.
[38] Thurner L, Muller A, Cerutti M, Martin T, Pasquali JL, Gross WL, et al. Wegener's granuloma harbors B lymphocytes with specificities against a proinflammatory transmembrane protein and a tetraspanin. J Autoimmun 2011;36:87–90.