Key advances in the clinical approach to ANCA-associated vasculitis

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Key advances in the clinical approach to ANCA-associated vasculitis

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Abstract | The updated nomenclature for vasculitis defines this varied group of disorders by aetiology, specific features of pathogenesis and clinical symptoms; diagnostic and classification criteria for clinical practice are in development. Here, I review some important advances in the management of vasculitis within the category of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which encompasses microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). The clinical approach to the management of the patient with AAV should include testing for ANCA specificity; proteinase 3 (PR3)-specific ANCAs are most often associated with GPA, whereas myeloperoxidase (MPO)-ANCAs are usually associated with MPA. Also important to the management of AAV is an assessment of the disease stage and severity, to enable tailored treatment based on an algorithm derived from controlled-trial data. Remaining questions pertain to the dosage and duration of corticosteroid treatment, the selection of patients for, and duration of, maintenance treatment after induction of remission, and the identification of safer and more effective therapies than are currently in use. Outcome measures should assess not only disease activity, but also damage and quality of life. Infections, cardiovascular events and malignancies also contribute to outcome, and their prevention should therefore be part of the clinical approach to managing patients with AAV.

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Introduction

Vasculitis is defined as inflammation of the blood vessels and can be aseptic or caused by invasion of the vascular wall by microorganisms. Aseptic vasculitis, in which infectious agents can be indirectly involved, is discussed here. The diverse clinical manifestations of noninfectious vasculitis are dependent on the location and size of the inflamed blood vessels and the immunopathogenesis of the lesions. As such, vasculitis is a clinically heterogeneous group of disorders. Even within a defined category, such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), clinical manifestations can vary widely and require different diagnostic and therapeutic approaches.

In this Review, I discuss the latest classification of vasculitis and the need for diagnostic criteria that can be used in clinical practice. Focusing on AAV, the relevance of disease stage and severity and the importance of distinguishing active disease from permanent damage will be discussed. The impact of correct assessment of disease stage, severity and activity on therapeutic choices, including short-term and long-term outcome, is also reviewed.

Classification of vasculitis

Many attempts, including the 1990 ACR criteria for the seven most prevalent forms of vasculitis, have been made to classify the vasculitis syndromes into homogeneous entities for use in research.[1,2] The 1990 ACR criteria were intended to classify patients with a confirmed diagnosis of vasculitis into specific syndrome subsets; however, they have widely been used as diagnostic criteria, consequently losing their specificity. That these criteria cannot be used as diagnostic criteria, and our evolving understanding of AAV, prompted a multidisciplinary group of clinicians and pathologists to convene the 1994 Chapel Hill Consensus Conference (CHCC), in an attempt to redefine the vasculitis syndromes by the size of the blood vessels affected, the immunopathology of the lesions and some clinical characteristics.[3] Since then, the CHCC nomenclature has often been used to define vasculitis syndromes and for inclusion of patients in clinical studies. However, the CHCC nomenclature was intended to be a resource for the creation of classification and diagnostic criteria, not to be used directly as diagnostic or classification criteria. The ACR criteria,[1,2] which were also not intended as diagnostic criteria, had further drawbacks, such as not including AAV or separating granulomatosis with polyangiitis (GPA) from microscopic polyangiitis (MPA). For these reasons, Watts *et al.*[4] developed an algorithm to classify patients with AAV and polyarteritis nodosa. This algorithm was validated,[5,6] and in 2012 was endorsed by the European Medicines Agency (EMA).[7,8]

Insights from vasculitis research over the past decade led to a 2012 revision of the 1994 CHCC nomenclature, focusing on aetiology, pathogenesis, pathology and

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Key points

- Aetiology, pathogenesis, pathology and clinical characteristics are the basis of the 2012 Chapel Hill Consensus Conference (CHCC) vasculitis nomenclature, and diagnostic and classification criteria for clinical practice are in development
- Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is now recognized by the CHCC nomenclature
- The clinical approach to managing patients with AAV should include assessing: if the patient has proteinase 3-specific or myeloperoxidase-specific ANCAs; the extent and severity of disease; and disease activity
- The dosage and duration of corticosteroid treatment as well as selection of patients with AAV for (and duration of) maintenance treatment are not well defined
- Preventive treatment of infections and cardiovascular risk factors will improve outcome
- Outcome measures should include not only disease activity, but also damage and quality of life

clinical characteristics as the basis for categorization.[9] Compared with the 1994 CHCC nomenclature[3] and the EMA-approved and validated tool,[7,8] the 2012 CHCC recommendations are a more thorough overview of vasculitis (Box 1). As well as categories based on the size of the blood vessels involved, four new primary categories are included: variable-vessel vasculitis; single-organ vasculitis; vasculitis associated with systemic disease; and vasculitis associated with "probable aetiology". Hopefully, further research will lead to the aetiological classification of more vasculitis subtypes and enable development of specific treatments. With respect to single-organ vasculitis, the 2012 CHCC recognized that over time, disease in one organ might develop into systemic vasculitis. Within the category of small-vessel vasculitis a distinction between AAV and immune-complex-mediated vasculitis was proposed. As in the 1994 CHCC, the three subcategories of AAV were also recognized: MPA, GPA and eosinphilic granulomatosis with polyangiitis (EGPA; Box 2). Partly as a result of general recommendations by the WHO International Classification of Diseases committee, the 2012 CHCC replaced some eponyms with descriptive terms. 'Henoch–Schönlein purpura' was replaced by 'IgA vasculitis' and 'Churg–Strauss syndrome' by 'EGPA'. By consensus, definitions were proposed for all the individual vasculitis syndromes.

In the future, this resource might be used for developing criteria for classification and diagnosis; importantly, the 2012 revision to the CHCC nomenclature still cannot be used for diagnosis and classification of individual patients. Furthermore, our currently evolving understanding of the pathogenesis of these syndromes might lead to further revisions. For example, GPA and MPA have different HLA class II associations, *HLA-DP* and *HLA-DQ*, respectively.[10] Even stronger, are the associations between these HLA class II genes and ANCA specific for proteinase 3 (PR3) and myeloperoxidase (MPO), respectively, suggesting that PR3-AAV and MPO-AAV, rather than GPA and MPA, are distinct diseases. A classification on the basis of autoantibody specificity has implications for stratification or even separation of patients within clinical trials.

Notably, patients with clinical features and histopathology consistent with AAV can test negative for ANCAs, particularly those with a limited form of GPA. In a cohort of 365 patients with GPA, only 11 tested negative for any specificity of ANCA and these patients all had GPA limited to the ear, nose and throat region (Table 1, unpublished observations). One study found that 32.9% of patients with pauci-immune crescentic glomerulonephritis were ANCA-negative and had fewer extrarenal symptoms than patients who tested positive for ANCAs.[11,12] Some patients who tested negative for ANCAs might have antibodies to lysosome-associated membrane glycoprotein 2 (LAMP-2), but data on the sensitivity and specificity of anti-LAMP-2 antibodies for pauci-immune glomerulonephritis are conflicting.[13,14] Interestingly, in 14 out of 21 patients who tested negative for ANCAs using conventional methods, antibodies specific for an MPO peptide were detected by serum IgG fractionation; these serum antibodies are masked by a fragment of ceruloplasmin (a natural inhibitor of myeloperoxidase).[15,16] Future studies should study if ANCA-negative AAV is restricted to limited forms of AAV that might become ANCA-positive when generalized AAV develops. Finally, only ~40% of patients with EGPA test positive for ANCAs, mostly for MPO-ANCAs. The clinical presentation of patients with ANCA-positive EGPA is better characterized by vasculitis manifestations, whereas tissue infiltration with eosinophils predominates in patients with ANCA-negative EGPA, suggesting that subsets of EGPA might be classified as different diseases (Box 3).[17–19]

Diagnostic criteria

As mentioned, the 2012 CHCC nomenclature of vasculitis syndromes only provides definitions and the ACR criteria are classification criteria. Diagnostic criteria are defining features of a particular disease that can be used to predict the emergence of disease in a particular patient.[9] 'Gold-standard' diagnostic criteria are generally based on expert opinion. For some of the vasculitis syndromes listed in Box 1, validated diagnostic criteria are available, but for most, including AAV, they are not. If available, as is the case for Behçet disease,[20] they are not unequivocally accepted. An ongoing large global study, the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study, is developing and validating diagnostic criteria for the vasculitis syndromes.[21] Until the results of this study are available, classification criteria can be used,[1,2,9] with the understanding that vasculitis should be diagnosed before applying the ACR criteria.[1,2]

Clinical assessment of AAV

Three items are relevant in the clinical approach to managing patients with AAV. The first relates to the stage of the disease process, the second to the distinction between active disease and damage, and the third to quality-of-life (QOL) assessment. Identification of the stage of disease is important in relation to treatment and prognosis as different therapeutic approaches have been proposed for limited (localized), early systemic, generalized, severe and refractory disease,[22] as defined by the European Vasculitis Study Group (EUVAS) and EULAR: 'limited disease' is usually restricted to the

Box 1 | CHCC 2012 nomenclature for vasculitis[9]

Large vessel vasculitis
Takayasu arteritis
Giant cell arteritis

Medium vessel vasculitis
Polyarteritis nodosa
Kawasaki disease

Small vessel vasculitis
ANCA-associated vasculitis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis

Immune-complex small vessel vasculitis
- Anti-glomerular-basement-membrane disease
- Cryoglobulinaemic vasculitis
- IgA vasculitis (formerly Henoch-Schönlein purpura)
- Hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis)

Variable vessel vasculitis
Behçet disease
Cogan syndrome

Single organ vasculitis
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis

Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others

Vasculitis associated with probable aetiology
Hepatitis C virus-associated cryoglobulinaemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune-complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis
Others

Abbreviation: CHCC, Chapel Hill Consensus Conference. Modified with permission obtained from Jon Wiley and Sons, Jennette, J. C. *et al. Arthritis Rheum.* **65**, 1–11 (2013).[9]

Box 2 | CHCC 2012 definitions of AAV[9]

GPA
Granulomatous inflammation usually involving the respiratory tract
Small-vessel necrotizing vasculitis
Necrotizing glomerulonephritis is common

MPA
Small-vessel necrotizing vasculitis
Necrotizing glomerulonephritis is very common
Pulmonary capillaritis often occurs

EGPA
Eosinophil-rich granulomatous inflammation of the respiratory tract
Small-vessel necrotizing vasculitis
Blood eosinophilia
Asthma

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; CHCC, Chapel Hill Consensus Conference; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

upper respiratory tract or the lungs; 'early systemic disease' presents without organ-threatening or life-threatening involvement; 'generalized disease' involves renal or other organ-threatening disease; 'severe disease' is defined as renal or vital organ failure; and 'refractory disease' is a progressive disease not responding to standard treatment.[16] In addition, 'grumbling disease' should be recognized as a condition with persistent disease activity frequently occurring in the nasal and paranasal mucosae.[23] In this case, the distinction between active disease, damage and infection is difficult and might require repeated biopsies.

Disease activity

An adequate tool for assessing disease activity in patients with AAV is the Birmingham Vasculitis Activity Score (BVAS), which categorizes organ involvement and disease activity in each organ system.[24] BVAS has been validated and used as an outcome parameter in many trials. The scoring system has been adapted and improved and the current version (BVAS-3) has been revalidated.[25,26] For GPA, a more specific disease activity score (BVAS/WG) has been proposed[27] and has proven sensitive to changes in disease activity in a large clinical trial.[28] Furthermore, outcome data from 535 patients with AAV showed that a high BVAS at presentation was a negative prognostic factor for patient survival.[29] For childhood vasculitis, generally, a specific activity score has been developed and preliminarily validated.[30] Classification, disease stage identification and assessment of disease activity are a basis for treatment.

Damage

When assessing disease activity, a distinction should be made between active disease and permanent 'damage'. The BVAS-3 system defines active disease as abnormalities due to vasculitis that are new or have worsened within the past 4 weeks. If these abnormalities persist without change for more than 4 weeks it is designated as persistent disease. Also, a vasculitis damage index (VDI) that records 'damage' since the onset of vasculitis has been developed and validated.[31] Damage, defined as "irreversible change resulting from scars",[31] should be present for at least 3 months and the VDI score can either increase or remain stable over time. Damage can be accrued due to vasculitis, its treatment or other comorbidities. As such, the VDI can be used as an outcome parameter in clinical trials, as has been recommended by EULAR.[32,33] Short-term (≤1 year) VDI data from 735 patients participating in six EUVAS trials, and long-term (mean 7.3 years) VDI data from 535 patients, are now available.[34] The data show that 34.5% of patients have ≥1 damage item at baseline, indicating that organ damage occurs soon after the first manifestation of vasculitis or before diagnosis. Early accrual of damage is also demonstrated by the presence of ≥1 item in 82% of patients at 6 months. Renal damage (glomerular filtration rate <50 ml/min) was more frequent in patients with MPA (60%) than those with GPA (32%) at long-term follow-up, whereas otolaryngeal damage, in particular nasal

Table 1 | Are ANCA present in all patients with AAV?

Diagnosis	PR3-ANCA	MPO-ANCA	Elastase-ANCA	No ANCA detected	% of patients with ANCA
GPA (n=364)	323	25	4	12*	96
EGPA (n=36)	0	23	0	13	64
MPA (n=85)	16	67	1	1	98
NCGN (n=54)	4	47	1	2	94

*10 of 12 were ENT-limited GPA. Unpublished data. Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibodies; ENT, ear nose and throat; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NCGN, necrotizing and crescentic glomerulonephritis.

Box 3 | Is EGPA two distinct diseases?

ANCA-associated EGPA*

Clinical associations
- Necrotizing glomerulonephritis
- Purpura
- Pulmonary hemorrhage
- Mononeuritis multiplex

Histopathology
- Small-vessel vasculitis

Pathogenesis
- ANCA-related

ANCA-negative EGPA*

Clinical associations
- Nasal polyposis
- Pulmonary infiltrates
- Cardiomyopathy
- Mononeuropathy or polyneuropathy
- Eosinophilic gastritis and enteritis

Histopathology
- Tissue infiltration with eosinophils

Pathogenesis
- Toxic products from eosinophils

*Despite these distinctions, there is still considerable overlap.[17–19] Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis.

blockade and crusting, was more frequent in patients with GPA (45% vs 5% MPA), as was hearing loss (33% vs 5% MPA). In both groups of patients there was hypertension (47% in MPA, 39% in GPA) and peripheral neuropathy (14% in MPA, 22% in GPA). Cardiovascular damage and pathology related to the use of corticosteroids, (steroid-induced type 2 diabetes, osteoporosis and cataracts) was also frequent. These data show the importance of including damage as an outcome measure and the relevance of early diagnosis and treatment as well as prevention of comorbidities in the follow-up of patients with AAV.

Quality of life

Other than assessment of actual disease activity and organ damage, quality-of-life (QOL) is another item that deserves attention when assessing patients with AAV. From the perspective of the patient, health-related QOL is an important outcome measure. A retrospective analysis using the Short Form 36 (SF-36) health survey showed that both the physical and mental component scores of SF-36 are low in patients with GPA.[35] Increases in these scores correlated modestly with a decrease in BVAS/WG scores. In contrast to patients who did not achieve sustained remission, whose SF-36 scores slightly decreased, sustained remission led to gradual improvement of the scores. Another multicentre case–control study compared QOL between patients with AAV and two age-matched and sex-matched control groups from the general population: healthy individuals and those with chronic diseases.[36] Compared with healthy individuals, QOL in patients with AAV was lower than that of healthy individuals, and was comparable to patients with chronic diseases, such as arthritis and kidney disease. QOL was associated with clinical variables such as serum concentrations of C-reactive protein and the use of prednisone, but the association was even stronger with biopsychosocial factors, in particular, fatigue. Treating biopsychosocial factors should therefore be included in therapeutic strategies for patients with AAV.

In combination with an assessment of the stage of the disease and recording disease activity and organ damage, QOL should be included in the clinical approach to managing patients suspected of having AAV. All these variables should be evaluated as outcome measures following treatment.

Therapeutic considerations

As I have already indicated, treatment of AAV should be based on the stage of the disease and its severity. Initial treatment should be aimed at induction of remission. The multicentre studies of the Vasculitis Clinical Research Consortium (VCRC) and EUVAS provided a therapeutic algorithm for patients with AAV.[22,37] This therapeutic approach for inducing remission has been reviewed elsewhere,[22,38–40] and a schematic representation of the current strategy is shown in Figure 1. Maintenance treatment in remission has also been reviewed.[22,40] With respect to the current therapeutic approach to the management of patients with vasculitis a number of items (outlined in the following sections) need to be considered.

Categories of AAV

In most therapeutic studies of AAV, patients are included irrespective of the specific category of the disease. Although EGPA is generally considered as a separate entity, patients with GPA and MPA, sometimes in different stages of the disease, are frequently categorized together. However, the genetic basis of MPO-AAV (which is mostly MPA) and PR3-AAV (mostly GPA) are quite different, suggesting that we are dealing with two different diseases.[10] Also, the clinical manifestations of GPA and MPA are different. Granulomatous inflammation is predominant in patients with GPA and not in those with MPA.[4] Studies have shown that, irrespective of the specific diagnosis, extrarenal organ manifestations and respiratory tract granulomas are more frequent in patients with PR3-AAV than in patients with MPO-AAV.[41,42] Furthermore, patients with necrotizing crescentic glomerulonephritis and PR3-AAV have more dramatic deterioration of renal function compared with patients who have MPO-AAV.[41,42] However,

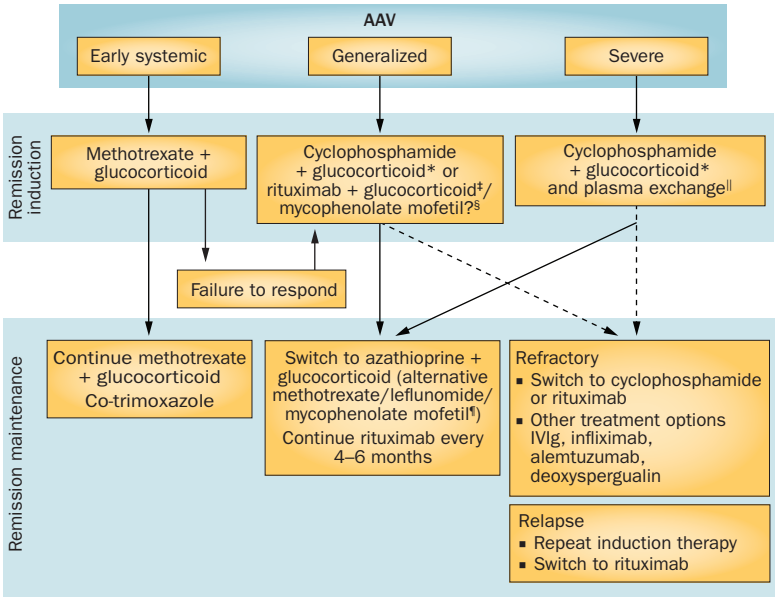

Figure 1 | Treatment strategies for remission induction and maintenance of AAV. Maintenance treatment should be continued for at least 18–24 months. Disease stages (early systemic, generalized, severe) are based on EUVAS and EULAR definitions.[32,37] *Add co-trimoxazole for prophylaxis of *Pneumocystis jiroveci* pneumonia. ‡Rituximab with low-dose cyclophosphamide or rituximab alone can be used instead of the regular dose of cyclophosphamide.[103] §Mycophenolate mofetil has been tested for noninferiority compared with cyclophosphamide for induction of remission; although indicative for efficacy, the study was underpowered to significantly demonstrate noninferiority.[104] ‖Long-term benefits of plasma exchange are unclear.[105] ¶Mycophenolate mofetil was less effective than azathioprine in preventing relapses.[106] Abbreviations: AAV, antineutrophil cytoplasmic antibody-associated vasculitis; EUVAS, European Vasculitis Study Group; IVIg, intravenous immunoglobulin. Figure reproduced with some modifications with permission from NPG. Treatment of ANCA-associated vasculitis. *Nat. Rev. Nephrol.* **10**, 25–36 (2014).[22]

renal survival is significantly worse in patients with MPO-AAV than in those with PR3-AAV (hazard ratio 2.1, 95 % CI 1.11–3.80, $P = 0.01$),[43] suggesting that MPO-ANCA-associated glomerulonephritis is less responsive to treatment or has a more smouldering course. In addition, patients with PR3-AAV relapse more frequently than patients with MPO-AAV. In one analysis of 502 patients with biopsy-proven renal AAV, the relapse rate of patients with PR3-ANCAs was almost double that of patients with MPO-ANCAs, and ANCA specificity predicted relapse independently of the specific disease category.[44] Also, data from the EUVAS studies showed that the presence of PR3-ANCA is independently associated with a higher risk of relapse.[45] The RAVE study of 197 patients with severe AAV found that induction therapy with rituximab in combination with corticosteroids and without maintenance treatment is as effective as induction therapy with oral cyclophosphamide and corticosteroids followed by maintenance treatment with azathioprine.[46,47] This study also showed that the relapse rate in patients with PR3-ANCAs was far higher than in patients with MPO-ANCAs, irrespective of the treatment group. Mahr *et al.*[48] analysed 673 patients with newly diagnosed GPA or MPA enrolled in five clinical trials. With respect to outcome, five different clusters of patients were identified: renal AAV with PR3-ANCAs (40%); renal AAV without PR3-ANCAs (32%); non-renal AAV (12%); cardiovascular AAV (9%); and gastrointestinal AAV (7%). These clusters differed in relapse rate and outcome, with more relapses in patients with renal AAV and PR3-ANCAs than in patients with renal AAV without PR3-ANCAs, but higher mortality occurred in the latter group.

Taken together, these studies show that PR3-AAV differs from MPO-AAV with respect to treatment response, relapse rate and outcome. Further trials should separately study patients with PR3-AAV and MPO-AAV. These studies should also test whether, with respect to classification, the terms 'PR3-AAV' and 'MPO-AAV' should be used instead of the current terms 'GPA' and 'MPA', respectively.

Interestingly, drug-induced vasculitis is most often associated with MPO-ANCAs. In particular, use of propylthiouracil, but also hydralazine and minocycline, are associated with small-vessel vasculitis and MPO-ANCAs, sometimes in combination with ANCAs specific for other neutrophil proteins, such as bactericidal permeability-increasing protein, cathepsin G, neutrophil elastase or lactotransferrin.[49] Levamisole-adulterated cocaine use is also associated with AAV, manifesting with fever, arthralgia and myalgia, ulcerating skin lesions and erosive upper airway disease; these patients often test positive for elastase-ANCAs, and for MPO-ANCAs and PR3-ANCAs, often simultaneously.[49,50] Why drug-induced AAV is particularly associated with MPO-ANCAs is not known.

Dose and duration of corticosteroid treatment

Various treatment regimens have been tested in controlled trials for induction of remission from AAV (Figure 1). All these regimens include corticosteroids, but differ in initial dose and tapering schedules. In 'generalized' disease, starting with 1g intravenous methylprednisolone on 3 consecutive days has been suggested, but not formally tested with respect to outcome, complications and adverse effects. This is usually followed immediately with 1 mg/kg oral corticosteroids daily (up to 80 mg per day), but again, this regimen is not based on evidence. The PEXIVAS trial is currently recruiting 500 patients with severe AAV to test the hypothesis that adjunctive plasma exchange, in addition to standard care, leads to a better outcome than standard care alone, and that a tapered reduced-dose glucocorticoid regimen is noninferior to a tapered standard-dose regimen.[51] Corticosteroids are important in the initial phase of (generalized) AAV in order to downregulate the severe inflammatory response. Experimental data suggest that the strong chemoattractant complement 5a (C5a) is important in this response.[52,53] A new trial will test the hypothesis that blocking the C5a receptor will reduce or eliminate the overall exposure to corticosteroids during induction.[54] Another item that has not been well studied relates to the tapering regimen of steroids. In order to reach complete remission, the RAVE study, unlike most other studies, required tapering of steroids to complete discontinuation at 6 months.[46,47]

Maintenance treatment: for whom and how long?

Once remission has been achieved, relapse of disease remains a risk, so maintenance treatment is recommended. The first drug regimen for remission maintenance therapy was 2 mg/kg oral cyclophosphamide continued for at least 1 year after complete remission was achieved and followed by tapering with 25 mg decrements every 3 months.[55] The benefit of maintenance treatment has, however, never been demonstrated in a controlled trial. It was shown that oral azathioprine was as effective as oral cyclophosphamide for maintaining remission,[56] and methotrexate can replace azathioprine in cases of intolerance.[57] However, despite maintenance treatment, ~15% of patients relapse during treatment.[56] This relapse rate increases to ~20–40% when the period following treatment-cessation is included, with a lower relapse-rate in patients who received oral cyclophosphamide for induction therapy (20.8%) compared with those treated with intravenous pulsed cyclophosphamide (39.5%).[57,58] The 18 month follow-up data from the RAVE trial are of interest in this respect.[46,47] Durable complete remission was defined as a score of 0 on a disease activity index, no use of corticosteroids, and absence of relapse or any other reason for treatment failure. Using these strict criteria, complete remission was present at 6, 12 and 18 months in 64%, 48% and 39% of patients in the rituximab group (without any maintenance treatment), respectively, and in 53%, 39% and 33% of patients in the cyclophosphamide (induction)–azathioprine (maintenance) group, respectively. Despite the absence of maintenance treatment in the rituximab group, relapses were no more frequent than in the cyclophosphamide–azathioprine group in which B-cell-depletion persisted even longer.

These data raise a number of questions. First, could we identify those patients who are at the lowest risk for relapse in order to avoid unnecessary maintenance treatment? As discussed, patients with PR3-AAV who have previously relapsed are at risk for further relapses. Furthermore, other biomarkers have been suggested to define outcome in AAV.[59] For example, an expanded $CD8^+$ T-cell memory population with expression of genes involved in the IL-7 receptor pathway and T-cell receptor signalling can be indicators of poor outcome in AAV.[60] Analysis of biomarker combinations could conceivably be used to decide whether or not patients with AAV should be given maintenance treatment; however, no controlled studies have yet shown this to be possible.

Second, how long should maintenance treatment be continued? The majority of relapses occur after stopping treatment. Unfortunately, no reliable markers to predict relapse are available. Persistence of ANCA after induction of remission (relative risk [RR] 9.0),[61] and an increase in ANCA-titre (sensitivity 79%, specificity 68%),[62] have been proposed as markers for relapse. But a lower risk of relapse in cases of persistence of ANCA after induction of remission (RR 2.6) was observed in a more recent cohort.[63] Furthermore, a meta-analysis of studies describing increased ANCA titres as a predictor of disease relapse showed a positive likelihood ratio of only 2.84 with a negative ratio of 0.49.[64] Data from the RAVE study showed that the absence of both B cells and ANCAs after treatment was associated with a low risk of relapse.[46] Also, another study showed that, after induction treatment with rituximab, relapses occurred only after natural reconstitution of B cells, and that this was either preceded by or was coincident with an increase in ANCA titres.[65] This raises the question of whether maintenance treatment with rituximab, based on analysis of B cells and ANCA titres, could provide a personalized approach for maintenance treatment of patients with AAV. One study showed that 2-year, fixed-interval rituximab retreatment (1g every 6 months) reduced the relapse rate from 73% to 11%.[66] Preliminary data from the French Vasculitis Study Group also showed that fixed-interval rituximab retreatment (0.5 g every 6 months) is better than azathioprine for preventing relapses.[67] Currently, EUVAS have a controlled trial comparing rituximab (1 g every 4 months) with azathioprine for maintenance of remission.[68]

Therapeutic approach to ANCA-negative AAV

Controlled, prospective studies on the treatment of patients with ANCA-negative pauci-immune crescentic glomerulonephritis are not available.[11] In general, the guidelines for ANCA-positive disease are also used for ANCA-negative disease.[12] Whereas prospective trials of rituximab treatment for ANCA-positive AAV included only patients with either PR3-ANCAs or MPO-ANCAs, successful rituximab treatment of patients with ANCA-negative GPA has been reported.[69] Within the spectrum of EGPA, ANCA-negative disease might be distinct from ANCA-positive disease, but this concept has not yet resulted in different therapeutic approaches.[70] Preliminary data suggest that blocking IL-5 (a potent inducer of eosinophils) with mepolizumab might be beneficial in treating EGPA, but no studies have dissected ANCA-negative from ANCA-positive EGPA.[71,72]

Comorbidities

Comorbidities are an important cause of mortality in AAV and contribute substantially to damage, as recorded by the VDI.[31] Comorbidities can be the result of disease, but are usually a result of treatment.[73,74] Major categories of comorbidities discussed here are infections, malignancies and cardiovascular events. Infections are the main cause of death during the first year (48%), but persist after the first year (20%) as a cause of mortality, together with cardiovascular disease (26%) and malignancy (22%).[29]

Infections

Major risk factors for infections are the use of corticosteroids, and lymphopenia and neutropenia resulting from the use of immunosuppressive drugs, in particular cyclophosphamide. High-dose corticosteroids and cyclophosphamide are independently associated with a high risk of infection.[75] Also, use of low-dose corticosteroids for more than 6 months is associated with a higher incidence of infections (0.64 per patient-year) compared with patients who were off corticosteroids

6 months after initiation of therapy (0.39 per patient-year).[76] A study from Canada showed that, other than the well-known risk of infection in individuals with neutropenia that is related mostly to the use of cyclophosphamide, lymphopenia is one of the strongest risk factors for infection.[77] In a retrospective analysis of 100 patients with AAV, most of whom were treated with cyclophosphamide and steroids, only 18% experienced neutropenia ($\leq 1.5 \times 10^9$/l), but 72% had episodes of moderate lymphopenia ($0.3–1.0 \times 10^9$/l) and 36% had severe lymphopenia ($\leq 0.3 \times 10^9$/l). The rate of severe infection was 1.00 per person-year with severe lymphopenia, and 0.08 and 0.10 for moderate and no lymphopenia, respectively, independent of other risk factors.

Other than common bacterial and viral infections, chronic nasal carriage of *Staphylococcus aureus* has been well-studied as a risk factor for relapse of GPA.[61] Maintenance treatment with co-trimoxazole not only reduces relapses of GPA by 60%, but also prevents common infections; median annual infectious episodes per patient were 0.0 in the co-trimoxazole group ($n = 41$) and 1.0 in the placebo group ($n = 40$; $P = 0.003$).[78] Whether this phenomenon is dependent on elimination of *S. aureus* has not been proven.

Opportunistic infections also have a major role. The risk of *Pneumocystis jirovecii* infection is particularly high during high-dose corticosteroid use, which can decrease cell-mediated immunity; prophylaxis with co-trimoxazole is mandatory for all patients treated with cyclophosphamide.[22] By contrast, the incidence of *P. jirovecii* pneumonia in patients with AAV treated with rituximab is low (1.2%), and does not support prophylactic treatment.[79]

Progressive multifocal encephalopathy (PML) is of particular concern for patients with AAV. Six patients have been described with AAV and PML, all were treated with cyclophosphamide and steroids.[80] PML has also been diagnosed in patients treated with rituximab for other autoimmune rheumatic diseases, in particular systemic lupus erythematosus and rheumatoid arthritis,[81] but not in rituximab-treated patients with AAV. However, vigilance is needed, and immunosuppressive therapy should be reduced or withdrawn if PML occurs.

In short-term studies of rituximab treatment for AAV, no major safety concerns, such as incidence or severity of infections, have been reported.[82] However, recurrent treatment with rituximab, reported in a study of 35 patients with GPA, resulted in hypogammaglobulinaemia in 30% of patients, constituting a strong risk factor for severe infections.[82] Herpes zoster frequently occurs in patients treated with immunosuppressive therapy for AAV,[75] and the current vaccine, a live-attenuated vaccine, should not be used in immunosuppressed patients.

General recommendations for vaccination of patients with autoimmune rheumatic diseases have been provided by EULAR.[83] Other than vaccinations, preferably given before immunosuppressive treatment is started, prevention of leukopenia and prophylaxis of *P. jirovecii* during cyclophosphamide treatment is advocated, and antifungal prophylaxis with fluconazole during high-dose corticosteroid treatment can be considered by the treating physician. Vigilance is warranted for any infection in patients with AAV.

Cardiovascular complications

In a 2012 systematic review, inflammatory bowel disease, AAV and infections (specifically HIV, pneumonia and urinary tract infections) were identified as risk factors for venous thrombosis.[84] A high incidence of venous thrombotic events in patients with AAV was first reported by Merkel *et al.*[85] and then confirmed in other cohorts.[86,87] As thrombotic events occur particularly during active AAV, prophylactic treatment should be considered for patients with concomitant risk factors for thrombosis.

Compared with the general population, the risk of coronary heart disease is twofold to fourfold higher, and stroke is also more frequent, in patients with AAV.[88–90] Within 5 years of diagnosis of GPA or MPA, 14% of patients will suffer from a cardiovascular event, with patients with PR3-ANCAs having a lower risk than those with MPO-ANCAs.[88] Subclinical atherosclerosis, independent of classical risk factors for cardiovascular disease, can be detected in many patients and can be caused by disease-related endothelial activation.[91] Furthermore, long-term use of corticosteroids can induce or aggravate metabolic syndrome as has been shown in patients with SLE.[92] Early control of inflammation together with control of classical risk factors for cardiovascular disease is essential.

Malignancies

Malignancies are of particular concern to patients with AAV. One study suggested that patients with AAV have an increased incidence of malignancies preceding or concurrent with diagnosis of AAV.[93] This retrospective study of 200 patients reported a RR of 6.02 (95% CI 3.72–9.74), but a case–control study of 293 patients with GPA could not confirm this finding, reporting a RR of 1.6 (95% CI 0.8–3.4) with some increase in non-melanoma skin cancers (RR 1.4, 95% CI 0.6–3.2) and testis carcinomas (RR 6.4, CI 1.1–38).[94]

Treatment-related malignancies are well studied in patients with AAV. Talar–Williams *et al.*[95] described the occurrence of bladder cancer in an observational NIH cohort of patients with AAV who were treated with cyclophosphamide. 50% of 145 patients from this cohort who had received oral cyclophosphamide for induction and maintenance treatment developed haemorrhagic cystitis and the estimated incidence of bladder cancer in these patients was 5% at 10 years and 16% at 15 years. Bladder cancer occurred only in patients with a history of nonglomerular haematuria and it was dependent on the cumulative dose of cyclophosphamide. These data were confirmed by a study from Sweden of 190 patients with AAV in which an 11-fold increase in bladder cancer occurred in patients who had used cyclophosphamide for at least 12 months,[96] and also by a study from France of 805 patients with AAV showing a standardized incidence ratio (SIR) of 5.00 for bladder cancer and an association of increased risk with the cumulative dose of cyclophosphamide and oral administration.[97] A more recent study

of 535 patients with AAV participating in EUVAS trials showed, however, a far lower SIR for malignancies. In this study the SIR for all malignancies was 1.58 (95% CI 1.17–2.08), 2.41 (95% CI 0.66–6.17) for bladder cancer, and 2.78 (95% CI 1.56–4.59) for nonmelanoma skin cancer.[98] This reduction in the occurrence of malignancies could be a result of a decrease in the use of cyclophosphamide: achieved by switching to alternative treatments; reducing cyclophosphamide dose; changing to azathioprine or methotrexate for maintenance treatment; and the use of intravenous pulse cyclophosphamide in combination with sodium 2-mercaptoethanesulphonate (mesna) and hyperhydration, instead of oral cyclophosphamide for remission-induction therapy.

Malignancies also occurred in the Wegener's Granulomatosis Etanercept Trial.[99] This trial tested the hypothesis that etanercept and the standard care could improve outcome in patients with GPA. In this trial of 180 patients, six patients developed solid malignancies in the etanercept group and none in the placebo group.[100] All six patients had previously been treated with cyclophosphamide, but this use did not differ between arms of the trial. Long-term follow-up data, available from 153 patients, showed a SIR for malignancies of 3.92 (95% CI 1.69–7.72) in the etanercept-treated patients, which was, however, not statistically different from the SIR of 2.89 (95% CI 0.94–6.73) for the placebo-treated patients.[101] Anti-TNF treatment of patients previously treated with cyclophosphamide might increase the risk of developing malignancies. The association between AAV, its treatment and malignancy was reviewed in 2013.[102]

Conclusions

The CHCC 2012 classification of vasculitis includes most, if not all, forms of vasculitis and has replaced some eponyms with more descriptive nomenclature. The ultimate intention is to base classification on aetiology and pathogenesis. A large study has been started to develop diagnostic and classification criteria that can be used in clinical practice.[21] The clinical approach to managing patients with vasculitis should include classifying the specific syndrome, assessing the stage of disease, its activity and organ damage as well as determining QOL. This method is a rational therapeutic approach, based on the results from controlled trials, with the possibility to assess individual short-term and long-term outcome. Better recognition of comorbidities (infections, cardiovascular events and malignancies) and their causes will lead to better prevention and treatment resulting in better outcomes for patients. Nevertheless, many questions remain unanswered, including those regarding the dosage and duration of corticosteroid treatment, the risk of relapse in relation to selection of patients for maintenance treatment, duration of maintenance treatment and the lack of sensitive and specific biomarkers to follow the development of the disease process and treatment responses. Answers to these questions will, it is hoped, further improve the outcome for patients with vasculitis.

Review criteria

The following review criteria have been used to identify English-language original and review articles in PubMed and SCOPUS from 1985–2014. Key words used were "vasculitis classification", "ANCA-associated vasculitis", "granulomatosis with polyangiitis", "Wegener's granulomatosis", "microscopic polyangiitis", "PR3-ANCA", and "MPO-ANCA". In relation to ANCA-associated vasculitis key words were "diagnosis", "prognosis", "outcome", "treatment", "infection", "malignancy", "cardiovascular events" and "atherosclerosis". References were included according to the author's opinion of their relevance to the subject.

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