Recent Aspects of Vasculitis and Future Direction

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Abstract

Vasculitis is pathologically identified as specific cellular inflammation, vessel destruction, and tissue necrosis. Current classifications of vasculitis such as the Chapel Hill Classification (CHCC) and American College of Rheumatology (ACR) guidelines are not sufficiently adequate for clinicians to diagnose vasculitis. The biomarkers that are currently in clinical use such as PR3-ANCA and MPO-ANCA, only help in diagnosing small vessel vasculitis and their sensitivity and specificity are not sufficient. However, recent developments related to the pathogenesis and etiopathogenesis of vasculitis have the potential to contribute to new and improved biomarkers. The determination of diverse roles of ANCA and synergistic effects of infection, genetic, environmental factors and drugs on pathogenesis is quite important. The demonstration of a new autoantibody directed to hLAMP-2 and the resemblance to some microbial structures, in addition to the determination of the possible roles of hepatitis B and C on vasculitis are important findings. These hints may lead to new biomarker developments, providing a better method to diagnose vasculitis. The evidence on T cell immunity as circulatory and lesional will likely contribute to the development of new drugs for vasculitis.

Key words: vasculitis, ANCA, pathogenesis, etiology of primary vasculitis

Introduction

Vasculitis is a pathologic and inflammatory condition causing the destruction of vessel walls, associated with many disease entities and characterized clinically by the types and locations of the affected vessels. Systemic vasculitis is rare with an incidence of 28 to 54 cases per million (1, 2).

Vasculitis is pathologically identified by the presence of cellular inflammation, vessel destruction, and tissue necrosis. The classification of systemic vasculitis has remained controversial in recent years. The Chapel Hill classification (CHCC) was not intended to establish diagnostic criteria. In addition, the criteria set forth by the American College of Rheumatology (ACR) were not designed to distinguish vasculitis from other diseases (3). Renal involvement, limb claudication, unequal blood pressure measurement, CNS ischemic symptoms, heart attack, mononeuritis multiplex, myalgias, skin lesions-purpuras, lung involvement-diffuse alveolar haemorrhage (hemoptysis), asthma-like symptoms, refractory chronic sinusitis, and other upper airway lesions are clinical scenarios suggestive of vasculitis (4, 5).

Some subsets of small vessel systemic vasculitis are categorized as ANCA-associated vasculitis (AAV) due to the determination more than 60% positivity of different types of ANCA.Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS) are specified by vasculitic lesions with little or no immunocomplex deposition and by anti-neutrophil cytoplasmic antibodies; these are known as ANCA-associated small vessel systemic vasculitis (AAV). Elevated ANCA blood titers are common in patients with multi-system involvement of small vessel vasculitis (6-8). It has also been proposed as a surrogate marker to predict disease relapse in patients who are currently in remission (9, 10).

New data suggest a pathophysiologic role of ANCA in the development of vasculitic disease. Although there are several hypotheses, the role of ANCA in vasculitis pathogenesis has not fully been elucidated. Environmental factors, genetic susceptibility, infections, physical agents, mechanical stress, septic and cholesterol emboli or drugs may endanger the integrity of vessel walls (11-15).

Recent studies have identified injury-associated signals...
and acute phase proteins upon activation of circulating leucocytes, platelets and endothelial cells. ANCA-associated vasculitis is ‘pauci-immune’, as tissue damage is apparently independent of the deposition of immune complexes or complement. Giant cell arteritis (GCA) and Takayasu’s arteritis (TAK) affect medium and large-sized muscular arteries possessing an internal elastic membrane and vasa vasorum. Cytokines are produced by activated T cells and macrophages in the vessel wall and along with reactive oxygen species are responsible for systemic manifestations and for local injury, which result in intimal hyperplasia, arterial occlusion and eventual end-organ ischemia (16-18).

The diagnosis of vasculitis depends on the competent clinician to recognize a combination of diverse clinical, laboratory, radiologic, and pathologic features (1, 4, 5). Researchers and clinicians are now able to better understand the etiology, pathogenesis and clinical scenarios by recent advances in the understanding of molecular mechanisms of vascular inflammation, genetics and immunologic findings. Clinicians require concrete methods beyond their special skills to diagnose patients and monitor remission and relapse of the disease by biomarkers for individualized therapy. Translations of preclinical data are important in developing new drugs and diagnostic biomarkers.

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**Epidemiology of Vasculitis**

Giant cell arteritis (GCA) is the most common type of vasculitis. The incidence of GCA is highest in populations of Scandinavian descent, affecting annually 15 to 35 per 100,000 people aged 50 years or older. Takayasu’s arteritis has a relatively constant global incidence of one to two per million. The ANCA-associated vasculitides have a total incidence of 20 per million with a peak age of onset at 65 to 74 years. Wegener’s granulomatosis seems to be more common in northern Europe than microscopic polyangiitis, which is more common in southern Europe and Japan. Henoch-Schönlein purpura (HSP) is the most common form of childhood vasculitis in the West with an incidence of 20 per 100,000 for those 17 years or younger, but it is rare in adults (13 per million). Kawasaki disease (KD) is most often seen in childhood populations of Southeast Asia; in Japan the incidence is 500 per million for children 5 years or younger, 50% of the cases occur in those under the age of 2 years old. Behçet’s disease occurs along the Silk Road and Mediterranean shorelines. The prevalence in Turkey is about 380 per 100,000. The various types of vasculitis have very different geographical and ethnic distributions, which provide some hints for the pathogenesis (19, 20).

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**Nomenclature of Vasculitis**

Two main classification systems have been used for many years. The 1990 ACR criteria that had the highest discriminating value to distinguish one syndrome from another were derived from analysis of a large number of systemic vasculitis cases. But, these criteria cannot distinguish vasculitis from other diseases and they did not include microscopic polyangiitis as a disease entity or ANCA as potential classification criteria (21-23). The CHCC definitions aimed to propose pathological definitions of each disease considered. However, the CHCC definitions are not a classification of diagnostic criteria (24). The concept of surrogate markers of vasculitis was therefore introduced, but a list of markers has not been well-defined. Sorenson et al defined a surrogate biomarker to CHCC definition for glomerulonephritis and granulomatous inflammation intended for clinical practice. On the other hand, the use of a single classification would lead to more unclassified patients and overlapping diagnosis (25).

Watts et al (26) recently proposed a new consensus algorithm for the classification of systemic vasculitis. They combined the ACR criteria with the CHCC definitions and Lanham criteria for CSS (26). The advantage of this algorithm simplified the clinical classification of AAV and periarteritis nodosa (PAN) for epidemiologic studies and as shown in the epidemiologic study of Liu et al. Watts’ algorithm could provide less unclassified patients and without overlapping diagnosis (27).

To date there is no published data distinguishing ANCA-associated disease from other vasculitides. Falk et al (11) proposed that the most general name for these diseases to be ANCA disease. If serologic data is known, then a disease may be further specified, such as PR3-ANCA disease, MPO-ANCA disease, or seronegative ANCA disease like SLE and RA. AAV is a problematic designation for limited Wegener’s granulomatosis or CSS and patients who have no evidence of vasculitis yet, thus these additional classifications may be helpful. Additionally, they recommended that clinicopathological phenotypes be designated ANCA granulomatosis (limited Wegener’s granulomatosis), ANCA granulomatosis with polyangiitis (GPA, Wegener’s granulomatosis), microscopic polyangiitis, or CSS. For example, granulomatosis polyangiitis further classified as PR3-ANCA GPA, MPO-ANCA GPA, or ANCA-negative GPA. These changes in nomenclature would permit the name of Wegener, a Nazi physician, to be discarded (11, 28). However, development of new diagnostic tools such as radiologic methods or several markers and collection of data utilizing these in clinical situations will pioneer the development of a new classification. Recently the European League Against Rheumatism (EULAR) placed consideration on this subject (29).

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**Pathogenesis of Vasculitis and Recent Aspects**

Pathogenesis is a crucial issue regarding differentiation of vasculitides. Large cell vasculitides are thought to be based on cell-mediated reactions and are not based on defined auto-antigens (30).

Immune complexes appear in some types of vasculitis such as Henoch-Schönlein purpura with IgA-containing immune deposits in the skin and kidney. Cryoglobulinemic vas-
culitis with hepatitis C infection is caused by the deposition of type 2 cryoglobulins in small vessels, similar to PAN-associated with hepatitis B. Deposition of IgM, IgG, and complement is seen in the postcapillary venule on biopsy samples from purpuric skin lesions of patients with leukocytoclastic angiitis. It has also been observed that drug induced-immune complex vasculitis and paraneoplastic vasculitis show immunocomplex deposition. In Wegener’s granulomatosis, CSS, and microscopic polyangiitis immune deposits have not been seen but deposits have been detected by electron microscopy in over half of the renal biopsy samples (1).

ANCA, when detected by indirect immunofluorescence on ethanol-fixed neutrophils, can have a cytoplasmic (cANCA), perinuclear (pANCA), or atypical staining pattern. Cytoplasmic staining is in most cases caused by autoantibodies to proteinase 3 (PR3-ANCA). A perinuclear pattern can be produced by antibodies to myeloperoxidase (MPO-ANCA), but also by antibodies to various other antigens from myeloid cells (31). CSS and microscopic polyangiitis patients usually have ANCA directed to myeloperoxidase (MPO), whereas in Wegener’s granulomatosis, ANCA is in most cases directed to proteinase-3 (PR-3). Most patients (70-80%) with Wegener’s granulomatosis are positive for PR3-ANCA, and few (10%) are positive for MPO-ANCA (31, 32). The majority of patients with microscopic polyangiitis (60%) are positive for MPO-ANCA, and some (30%) are positive for PR3-ANCA. A few patients with either Wegener’s granulomatosis or microscopic polyangiitis are ANCA-negative. In Wegener’s granulomatosis, these ANCA-negative patients mostly have localized disease, although some of these patients might develop ANCA once the disease progresses into a generalized form. In CSS, only 40% of patients are MPO-ANCA positive.

Interestingly, ANCA-positive CSS manifests clinically as mononeuritis multiplex, purpura and glomerulonephritis, whereas the ANCA-negative patients with CSS predominantly show tissue infiltration by eosinophils (33, 34). This observation suggests that CSS exists as two distinct disease entities.

PR3-ANCA and MPO-ANCA are, therefore, markers for different phenotypes of disease. PR3-ANCA-positive patients have much more granuloma formation in their lesions; involvement of more organs; a faster decline in renal function; and more frequent relapses compared with MPO-ANCA-positive patients (35-37).

Cellular and humoral immunity are involved in systemic vasculitides. The production of ANCA is the distinctive characteristic of AAV. However, T-cells, macrophages and other components of the immune system have been implicated in causation of disease. Additionally, pathogenic T lymphocyte responses and granuloma formation are present in GCA and Takayasu arteritis.

**Implications of T-cell immunity as lesional and circulatory especially in ANCA-associated vasculitis pathogenesis**

Circulating CD4+ CD25 T-cell population increases in AAV (36-39). These T-cells subsets are activated T-cells as well as Tregs (regulatory T cells) (38). Abdulahad et al reported an increase of CD25 high (Treg) CD4 T cells and CD25 low (activated T effector cells) cell populations in patients with Wegener’s granulomatosis. In addition, they demonstrated a functional impairment of CD25 high Tregs in these patients (39). Factors influencing Treg homeostasis and function might be involved in the pathogenesis of AAV, like leptin. Interestingly, decreased levels of leptin were found in patients with Wegener’s granulomatosis and MPA during active disease and normalized again when entering remission. Low levels of leptin during active disease may lead to Treg expansion, restoration of tolerance and attenuation of inflammatory response (40-45).

Memory T-cells are also expanded in AAV. Aberrant T-cell co-stimulation and T-cell senescence may have a role in expansion of this population. Thus, the breakdown of self-tolerance might be caused by memory T-cells (36). T-cells in AAV exhibit an altered expression pattern of co-stimulatory molecules. CD28 is downregulated on circulating and lesional CD4+ T-helper cells in AAV. The co-stimulatory molecules CD80 and CD86 are up-regulated on T-cells in Wegener’s granulomatosis after in vitro stimulation.

An increased expression of CTLA-4 (cytotoxic T-lymphocyte antigen 4) on CD4+ cells has been reported in Wegener’s granulomatosis (46-48). T-cells in AAV are constitutively active both during active disease and remission (49). In KD (Kawasaki disease) T-cell regulation and activation has also been identified, specifically co-stimulation, the second signal regulating optimal T-cell activation as the critical regulator of susceptibility to and severity of disease (50).

There are differences in Teff (T effector cells) type 1/type 2 polarization depending on the disease type and stage. CSS seems to be associated with Th2 polarization similar to asthma. Kiene and colleagues found higher levels of IL-4 and IL-13 in CSS than in Wegener’s granulomatosis. Soluble CX3CL1 levels and CX3CR1 expression on circulating T-cells correlate with disease activity. CXC3CL1 is a chemokine associated with a preferential Th1 response. Localized Wegener’s granulomatosis is associated with preferential Th1 response whereas Th2 responses are common in systemic disease (51-53). S-Ag (soluble retinal antigen) specific T-cells are present in certain active Behcet disease (BD) patients, and most of them are activated memory CD4+ T-cells. These T-cells may be involved in the pathogenesis of BD via producing Th1-dominant cytokines (54).

Monitoring Th17 and Th1 levels can aid in assessing disease activity in GCA (55). A patient with WG in remission typically has an increased number of circulating Th17 cells.
The role of ANCA in different views of pathogenesis of vasculitis

Some evidence supports the pathogenic role of ANCA in the clinical setting. Several longitudinal clinical observations have shown a relationship between increases in levels of PR3-ANCA and the occurrence of relapses. Finkelman et al (62) found increased levels of PR3-ANCA in some patients during relapse in their Etanercept trial (63) and ANCA began to decrease following their Etanercept treatment. On the other hand, Boomsma et al (64) did not find similar increases in the levels of PR3-ANCA followed by relapse (specificity 68%). Finally, Bansal and Tobin (65) reported a case of neonatal microscopic polyangiitis in a child born to a mother with MPO-ANCA (62-66).

In vivo and in vitro support comes from effects on pathogenesis of AAV in experimental models of ANCA with promising treatments and the implications of infections on the pathogenesis of vasculitis

After discovering that primed neutrophils can be activated by ANCA, other research groups demonstrated that both MPO-ANCA and PR3-ANCA antibodies are capable of activating neutrophils and monocytes through Fcϒ (in particular FcγRIIa and FcγRIIb) surface receptor involvement which initiates signal transduction pathways. Based on prior observations, Schreiber et al observed that ANCA-induced neutrophil activation is fundamental in the pathophysiologic mechanism in MPO-ANCA-associated vasculitis by blocking the action of enzyme phosphoinositol-3-kinase-ϒ, inhibiting the development of disease in an animal model of MPO-ANCA-associated glomerulonephritis. They focused their treatment by using inhibitors of this enzyme (67-69).

The role of complement system showed that blocking the C5a receptor on neutrophils could abolish lesion development in an animal model of MPO-ANCA glomerulonephritis. C5a could be a novel treatment of ANCA-associated vasculitis (70, 71). Necrotising vasculitis in AAV’s is characterized by neutrophil endothelial interaction within the vessel. ANCs stimulate neutrophil-induced cytotoxicity toward endothelial cells. MPO-ANCAs reduce leukocytes rolling over the endothelium and augment adhesion and transmigration across the endothelium. Blocking Fcϒ receptors and β2 integrins can inhibit this process (72, 73).

Kessenbrock et al showed that neutrophil activation by ANCA induces the generation of neutrophil extracellular traps (NETs) which contain PR3 and MPO. NETs can adhere to the endothelium and damage these cells. Moreover, they can activate plasmacytoid dendritic cells promoting local production of ANCs at the site of inflammation. NETs may not only trigger vasculitis in kidneys but may also promote an autoimmune response to PR3 and MPO (74).

These in vitro findings are supported by in vivo experimental models. When the spleen cells from immunized mice were transferred into immunodeficient or healthy mice, the recipient developed pauci-immune necrotizing crescentic glomerulonephritis (NCGN) and hemorrhagic pulmonary capillaritis (75). Neutrophils are necessary for lesion development as shown by Schreiber et al within irradiated (neutrophil depletion) MPO++/+ mice. The complement system proved essential to lesion development. Mice deficient in C5 and complement factor B did not demonstrate NCGN (76, 77).

Modulation of IgG glycosylation with bacterial enzyme EndoS can prevent induction and mitigate disease expression in an animal model of MPO-ANCA-associated glomerulonephritis. This could be a potential new approach in the treatment of ANCA-associated vasculitis (78).

Experimental studies strongly suggest that MPO-ANCs are pathogenic in AAV but the in vivo evidence of a pathogenic role of PR3-ANCA is less clear. After transferring developed anti-PR3 antibodies into naive mice, no signs of vasculitis developed in the kidneys and lungs. The only observation was increased tumor necrosis factor-α-induced local inflammation in the skin of anti-PR3 transferred mice (79, 80).

Why is PR3-ANCA alone not capable of inducing vasculitis?

Falk et al (11) suggest that another synergistic factor, an in vivo antecedent inflammatory process, such as a respiratory tract infection could provide the necessary cytokines for increased autoantigen availability. Increasing evidence indicates effector T-cells are involved in the pathogenesis associated with Wegener’s granulomatosis. This opens future directions to clarify the mechanisms underlying the relationship between Staphylococcus aureus and AAVs. Patients with nasal carries of S. aureus in Wegener’s granulomatosis have higher relapse incidences. ANCA positivity has been reported in patients with bacterial endocarditis some of whom develop features of vasculitis. S. aureus was the causative organism in these bacterial endocarditis cases. A protein complementary to PR3 may induce PR3-ANCA as
Pendergast et al (81) observed in some patients with PR3-ANCA. AAV patients have several antibodies against PR3. They suggested that antibodies to cPR3 could induce the antibody response to PR3 via idiopathic-antiidiopathic interreaction. Interestingly, they noticed that cPR3 shows homology with several microbe proteins including peptide-derived S. aureus. More recently, Yang et al described T-cells in the peripheral blood of patients with PR3-ANCA AAV reacting with cPR3 (11, 66, 81, 82).

Although rodents immunized with S. aureus do not developed AAV, immunization with E. coli did induce AAV in a small portion of animals. Recently, Kain et al presented a new autoantibody directed to hLAMP-2 (autoantibodies to another neutrophil protein) in pauci-immune necrotizing glomerulonephritis that is highly sensitive and specific for this condition. Interestingly, LAMP2 has homology to a protein expressed by fimbriated bacteria e.g gram-negative bacteria (FimH). Immunization of rats with FimH yielded antibodies to both FimH and hLAMP. However, the relationship between gram-negative bacteria and onset of AAV requires further studies (83, 84).

Infections may trigger other vasculitides such as small vessel vasculitis. Although its etiology is not unknown, there are data to support roles for hepatitis B and reports of higher frequency of exposure to Parvovirus B19 and cytomegalovirus in periarthritis nodosa patients. HIV also complicates PAN-like disease (85-89). Hepatitis C infection is suggested to play a causative role in some mixed cryoglobulinemia vasculitis cases. Some evidence suggests that these viruses induce direct vessel damage via immune complex formation (90-92).

**Genetic implications of vasculitis**

Infections can trigger the onset of vasculitis either independently or on the foundation of genetic susceptibility. There are some hints from genetic and epidemiologic studies. The increased risk in family members of WG has been well characterized. The genes with variants most strongly associated with AAV, the MHC and PTPN22 genes, also have variants associated with other autoimmune diseases. Different variants within each gene may be associated with different polymorphisms, for example AAV is associated with rs41295061. Aberrant transcription of neutrophil genes, a consequent loss of epigenetic silencing of MPO and PR3 in small vessel vasculitis patients, can be a synergistic factor in this disease (11, 93-96). Additionally, a number of polymorphisms have been identified in KD from medium-size vessel vasculitis and genetic susceptibility is important for the development of coronary artery aneurysms. Furthermore, there is some evidence that a bacterial toxin causes KD (97-99).

Genetic factors and infection can trigger each other. However, there can be other causative factors that induce the genetic predispositions and lead to vasculitis. Epidemiological evidence suggests that AAV is more common in people chronically exposed to environmental toxins including pesticides, livestock, high solvent exposure, asbestos, hydrocarbon fumes, and silica. Silica exposed patients typically have the clinical syndrome of MPO rather than PR3 (100, 101).

**Drugs can be another cause of AAV**

There is persuasive evidence that therapeutic drugs can induce AAV. Cutaneous leukocytoclastic vasculitis (hypersensitivity vasculitis) was found to be the most common cause in drug induced vasculitis. There are many drugs that are reported as a cause of vasculitis including antibiotics, non-steroidal drugs, methotraxate, azothiopurine, etanercept, cyclosporine, allopurinol, sulfasalazine, gold salts, anthyroid agents, anticonvulsants, antiarrhythmics, diuretics, leukotriene modifiers, and retinoids. Additionally, AAV has been reported after treatment of hydralazine for hypertension and penicilamine for rheumatic disease, in both cases with pANCA-associated focal necrotising glomerulonephritis. Recently, rifampsin and pyrazinamide-induced cutaneous vasculitis was reported to improve upon withdrawal of the medication in contrast to the tuberculosis-related vasculitis.

Continued use of the drug inducing vasculitis can lead to irreversible and life-threatening vasculitic organ damage (end-stage renal disease or pulmonary hemorrhage) (93, 102-105). COX-2 inhibitors can also cause fatal allergic vasculitis. CSS has been described in a small number of patients taking Cys LT1 antagonists. It is quite probable that this disease appears as a consequence of an un-masking effect with corticosteroid discontinuation (106, 107).

**Other immunologic aspects, mechanisms of vascular inflammation and remodelling in systemic vasculitis**

GCA and Takayasu arteritis affects large sized muscular arteries, wrapped with internal elastic membrane and vasa vasorum. Cytokines, produced under the guidance of dendritic cells (DC) that activate T cells and macrophages in the vessel and reactive oxygen species are responsible systemic manifestations. Inflammation elicited in response to vessel injury is required for the repair of the vessel wall, with eventual healing in short, vascular remodelling. Vascular remodelling in persistent inflammation can disrupt the mechanical performance of the vessel, leading to aneurysm formation or can deteriorate perfusion of peripheral tissues with end-infarction or hemorrhage. Eventually, arteries use MyD88 adaptor protein-dependent low-grade inflammation to alter their size, by regulating both their diameter and thickness of the wall layers dependent on changing blood flow. Alterations in hemodynamics in the vessel result in vascular remodelling with persistent structural changes (108, 109).

Recent reviews described the molecular and functional characteristics of the danger signals, which in addition to being released during necrosis, favour tissue repair, DC maturation and T cell- dependent immunity (see above). The high mobility group box 1 (HMGB1) is a small nuclear protein. Mechanical or immune-mediated injuries and tissue
ischemia/reperfusion all cause HMGB1 release. HMGB1 attracts endothelial cell precursors, which favor neovascularisation regulates activation, migration and function of DCs. DCs play a critical role in the establishment of ANCA and GCA inflammation. HMGB1 also plays role in vessel remodelling during large artery vasculitis. High levels of circulating HMGB1 characterize patients with systemic small vessel vasculitis, also (110-115).

Future Perspectives of Vasculitis

EULAR recommends some points for future classification. Predominant vessel size remains a major discriminating factor. However, there is not always a predominant vessel size such as in Behcet disease, Cogan’s syndrome, central nervous system vasculitis and relapsing polychondritis. Although there are types of medium size vessel vasculitis, such as KD and PAN, but sometimes they may have both vessel sizes. Atherosclerosis was suggested as a non-inflammatory vasculitis. However, this suggestion is inconclusive. There are several studies to demonstrate inflammatory mechanisms in atherosclerosis. Age is a worthy point in the definitions but not in all definitions (HSP and KD are in childhood but they are rarely seen in adults). TAK (Takayasu arteritis) is present several years after disease onset. Secondary vasculitis includes vasculitis due to infection, drugs, malignancy and connective disease. Primary entities move into a secondary category. The knowledge of specific etiologies in vasculitis continues to expand. Hepatitis B, C, several viruses, and bacteria can cause vasculitis. However, infection can be solely responsible for primary vasculitis. It will be important to enhance our knowledge of infectious effects on vasculitis. The new classification must facilitate the clinician’s decision for diagnosis. The available evidence is insufficient to make definite recommendations for diagnostic criteria. The collection of evidence from new radiologic techniques (CT, MR, PET, angiography), validated diagnostic and classification criteria and collaborations with clinicians, patients, researchers are urgent requirements to better understand, diagnosis and treat vasculitis (20, 29, 85, 116-124).

The separation of remission and relapse in vasculitis is a crucial issue. The Birmingham Vasculitis Activity Score is an efficient approach that can predict relapse and remission. However, it does not ensure that patients will stay in remission. In vasculitis, there is a need for standardized clinical tools or a surrogate marker to assess disease activity, damage and function. There are no universally applicable serological markers to assess disease activity or outcome. Additionally, we need to discover the mechanisms under relapse and long-term remission for preventing redundant immunosuppressive therapy (125-127).

Understanding these mechanisms will provide a better understanding of the drugs currently used and contribute to the development of new drugs in clinical trials. The development of new surrogate markers should provide a practical application diagnosis without biopsy. Additionally, new biomarkers can aid in diagnosing vasculitis related to drugs and to help better classify the disease state. Some patients with small-vessel vasculitis do not have ANCA positivity. Falk et al (11) suggest the new nomenclature to be “sero-negative ANCA disease”. This group is also interested in new biomarker research. LAMP2 antibodies, the relationship between infection and vasculitis might provide a better understanding to the pathology and aid in the development of a new biomarker. The understanding of the immunological basis of vasculitis will provide more effective treatment. The diversity of clinical situations, different behaviours for relapse and remission require research on genetic and environmental factors. Additionally, patients who tend to relapse can be determined before therapy and treated with targeted therapy. A well-regulated patient record network can be created and searched with new biomarkers from animal models to aid in understanding the pathogenesis and mechanisms in addition to developing effective therapies (11, 84, 106).

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References


