Small-Medium Vessel Vasculitides: is the Complement System a Potential Forgotten Target?

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ABSTRACT: Systemic vasculitides are a group of uncommon diseases characterized by blood vessel inflammation. The complement system is involved in the pathogenesis and clinical manifestations of several autoimmune diseases, including systemic vasculitides. This enzymatic system is a component of the innate immune system. Its main function was initially believed to be limited to the recognition and elimination of pathogens, but research in recent years has demonstrated the important role that complement proteins play in modulating adaptive immunity and in bridging innate and adaptive responses. Its activation is also critical for the development of T cell immunity and natural antibodies as well as for the regulation of autoreactive B cells. In systemic vasculitides, particularly small-medium vessel vasculitides, the complement system has been shown to contribute to the development of inflammatory damage. In view of these crucial functions, the complement system represents an attractive therapeutic target for a wide range of diseases, including vasculitic disorders.

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The systemic vasculitides are a group of uncommon diseases characterized by blood vessel inflammation. The reported annual incidence of these relatively uncommon disorders is 40–54 cases per 1 million persons [1]. The incidence appears to be affected by geography, age, and seasonal factors. Vasculitis may be limited to skin or other organs, or it may be a systemic disorder with multiple manifestations [2].

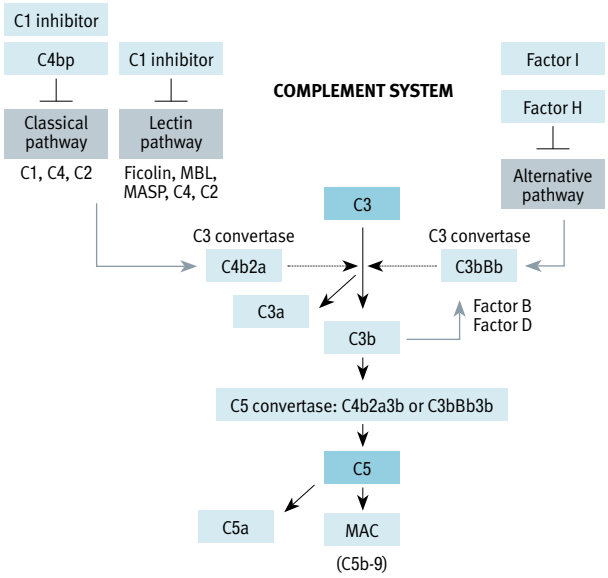
Complement is a part of the innate immune response, involved in adaptive response and crucial functions of the immune system

Since there are no diagnostic criteria for the primary systemic vasculitides, physicians must rely on experience and disease definitions. Recently, the Chapel Hill Consensus Conference (CHCC 2012) nomenclature defined 10 primary vasculitides based on vessel size (large, medium, small). In particular, the CHCC 2012 adopted the recommendations of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism (EULAR) to replace 'Wegener's granulomatosis' with 'granulomatosis with polyangiitis' (GPA) [3]. Churg-Strauss syndrome was replaced with the term 'eosinophilic granulomatosis with polyangiitis' (EGPA) to provide continuity within the anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis group. Henoch-Schönlein purpura was now named 'IgA vasculitis' (IgAV) based on the established evidence that the defining pathological feature is abnormal immunoglobulin A deposition in vessel walls [3].

The pathogenesis of these diseases is characterized by the presence of leukocytes in the vessel associated with the production of wall inflammatory damage. Depending on the specific vasculitic disorder, affected vessels vary in size, type and location. Many vasculitic disorders are caused by immune complexes (IC), which implies that the activation of the complement system is a pathogenic mechanism. The complement system is a component of the innate immune system, which includes physical, cellular and chemical elements [4]. Its immunoregulatory functions were recently demonstrated: i.e., the complement proteins play an important role in modulating both adaptive and innate immunity responses. This enzymatic system comprises more than 30 plasma and membrane-bound proteins [4]. The activation of these proteins occurs through three pathways: classical, alternative, and lectin. All three pathways are activated according to a cascade system, with activation of one factor leading to the activation of the next [Figure 1]. The contribution of complement to the development of inflammatory damage was confirmed through a series of elegant studies, with a body of accumulated data demonstrating that the activation of the complement system is also critical for the development of T cell immunity, the development of natural antibodies, and the regulation of autoreactive B cells [4,5].

The diagnosis of vasculitides relies on the recognition of a compatible clinical presentation supported by specific laboratory or imaging tests and confirmatory histology. ANCA testing has been especially valuable in defining a subgroup of small vessel vasculitides. Treatment is based on clinical manifestations and level of organ involvement. Evidence on traditional immunosuppressive therapies, such as methotrexate and cyclo-

Figure 1. Activation of the complement system. Activation of the complement system occurs through three pathways: classical, alternative, and lectin. All the pathways lead to the cleavage of C3 and finally converge at the activation of C5, with possible formation of the membrane attack complex (MAC). To avoid excess complement activation the complement system is tightly controlled by several regulatory proteins (including C1 inhibitor, C4 binding protein, Factor I, Factor H shown in the figure) that act at different points of complement cascade



phosphamide, has been collected. Newer approaches, e.g., the use of anti-tumor necrosis factor-alpha (anti-TNFa) or anti-B cell therapies, are being tried in refractory cases [6].

ANCA-ASSOCIATED VASCULITIDES

The ANCA-associated vasculitides (AAV) are a group of diseases with predominant inflammation of small vessels and the presence of detectable ANCA in serum. Due to common features, it is accepted that AAV share common pathogenic mechanisms. A new nomenclature has recently been introduced, with AAV including GPA, microscopic polyangiitis (MPA), EGPA and renal limited vasculitis [2]. Research on AAV has shown significant advances in the last two decades. Environmental toxins have been implicated, such as silica, a potential activator of the inflammasome complex that, among other functions, generates the active cytokine interleukin (IL)-1 [7]. Infections due to several microbes including *Staphylococcus aureus* have been linked repeatedly to the pathogenesis of vasculitis. Toxin from *Staph. aureus* is a potent activator of the NLRP3 inflammasome, suggesting potential links between different environmental agents and their pro-inflammatory effects in vasculitis. Infection has also been implicated in the formation of ANCA, specifically lysosomal-associated membrane protein 2 (LAMP-2) [8]. Homology between the middle portion of the complementary proteinase 3 (cPR3) sequence and *Staph. aureus* proteins may induce anti-complementary PR3 antibodies that, in turn, induce anti-PR3 antibodies via an anti-idiotypic response and ANCA vasculitis. These small vessel vasculitides are characterized by necrotizing inflammation of the vessel wall, particularly of small arteries, arterioles, capillaries and venules, in conjunction with the presence of ANCAs [9]. ANCAs are autoantibodies produced in response to neutrophil cytoplasmic enzymes and represent a useful marker for the diagnosis of systemic vasculitis such as GPA, MPA and EGPA. These autoantibodies can be detected using immunofluorescence assay (IFA) and are classified according to dyeing patterns into cytoplasmic-ANCA (c-ANCA) or perinuclear-ANCA (p-ANCA). Enzyme-linked immunosorbent assay (ELISA), currently the most popular assay, can detect myeloperoxidase (MPO)- and proteinase 3 (PR3)-ANCAs [10].

The majority of p-ANCAs and c-ANCAs have been proven to be equivalent to MPO- and PR3-ANCAs, respectively. Patients with MPA (50–80%) and EGPA (2–50%) are positive for p-ANCA, and those with GPA (75–90%) are positive for c-ANCA. However, a small percentage (5–20%) of GPA patients may have p-ANCA, while positivity for c-ANCA may be observed in 10–50% of MPA and 3–35% of EGPA patients [11]. In patients with active systemic GPA, MPA or EGPA, ANCAs are reported to be positive in over 80%, 70% or 50% of cases, respectively [10]. In particular, however, some patients are negative for both MPO- and PR3-ANCAs while other clinical findings strongly suggest the presence of systemic vasculitis, which makes diagnosing systemic vasculitis insidious [10]. In addition to the role of autoantibodies, T cells also participate in disease mechanisms. T cells are localized in inflammatory lesions related to AAV, and granuloma formation is considered T cell dependent [12]. In this respect, alterations of T cell immunity such an abnormal T cell activation and dysfunction of T regulatory cells have been described [13].

Complement participates in the pathogenesis of several small-medium vessel vasculitides including ANCA-associated vasculitides, cryoglobulinemia, urticarial vasculitides and IgA vasculitis

In AAVs, the adaptive immune response, embodied by the ANCAs, interacts with innate immunity, especially with neutrophils and the complement system. Together, these elements target the endothelium, causing necrotizing vasculitis [14]. Among the different soluble mediators involved in ANCA vasculitis, components of the alternative complement pathway are emerging as forerunners since the elegant demonstration of protection from disease in C5 and factor-B knockout mice. In vitro data demonstrate that in AAVs the complement system

constitutes an amplification loop for ANCA-induced neutrophil activation. Schreiber et al. [15] showed that supernatants from ANCA-activated neutrophils activate the complement system via the alternative pathway, resulting in the production of C5a, among others [15]. C5a was able to prime neutrophils for ANCA-induced activation, and blocking the C5a receptor on neutrophils abrogated this process.

Murine models have shown that complement depletion prevented MPO-ANCA glomerulonephritis, and mice deficient in C5 or complement factor B did not develop pauci-immune necrotizing crescentic glomerulonephritis, characterized by the relative lack of immunoglobulin and complement deposition on kidney biopsy immunofluorescence [15]. In agreement with these experimental data, the complement components MAC (membrane attack complex), C3d and factor B could be detected in diseased glomeruli of patients with AAVs. The alternative pathway component factor B co-localized with MAC, but the classical pathway component C4d could not be detected [16]. Interestingly, AAV in the kidney is not quite so pauci-immune as once thought. Although immune complexes containing IgG or IgA are generally lacking in the classic lesions of ANCA-associated glomerulonephritis, non-specific IgM deposits and certainly complement deposition are often present. The anaphylatoxin C5a not only primes neutrophils for an ANCA-induced respiratory burst, but C5a receptor-deficient animals are protected against development of glomerulonephritis [15]. AAV are not associated with hypocomplementemia. Moreover, serum C3 and C4 levels are not a sensitive indicator of complement involvement because certain forms of glomerulonephritis and vasculitis that have substantial vascular deposits of complement are not associated with hypcomplementemia. According to these findings, compounds interfering with the complement cascade should be explored as therapeutic options for AAV. The pathogenesis of AAVs is summarized in Figure 2.

In vasculitic disorders, the complement system could be a possible target for therapeutic purposes

CRYOGLOBULINEMIC VASCULITIS

Cryoglobulins (CG) are an abnormal group of serum proteins that share the common property of reversible precipitation at low temperatures. The majority of CG are either intact monoclonal immunoglobulins or immune complexes in which one component, usually IgM, exhibits antibody activity to IgG. The latter are known as mixed CG [17]. Cold-precipitate, monoclonal or polyclonal immunoglobulins can occur in a variety of diseases, including plasma cell or lymphoid neoplasms, chronic infection, and inflammatory diseases. With the discovery of the hepatitis C virus (HCV), it became established that the majority of cases of cryoglobulinemia are related to HCV infection [Figure 3]. Essential mixed cryoglobulinemia demonstrates a prominent association with HCV infection (> 90%). It is a systemic vasculitis (leukocytoclastic vasculitis) affecting cutaneous vessels and multiple visceral organs [18].

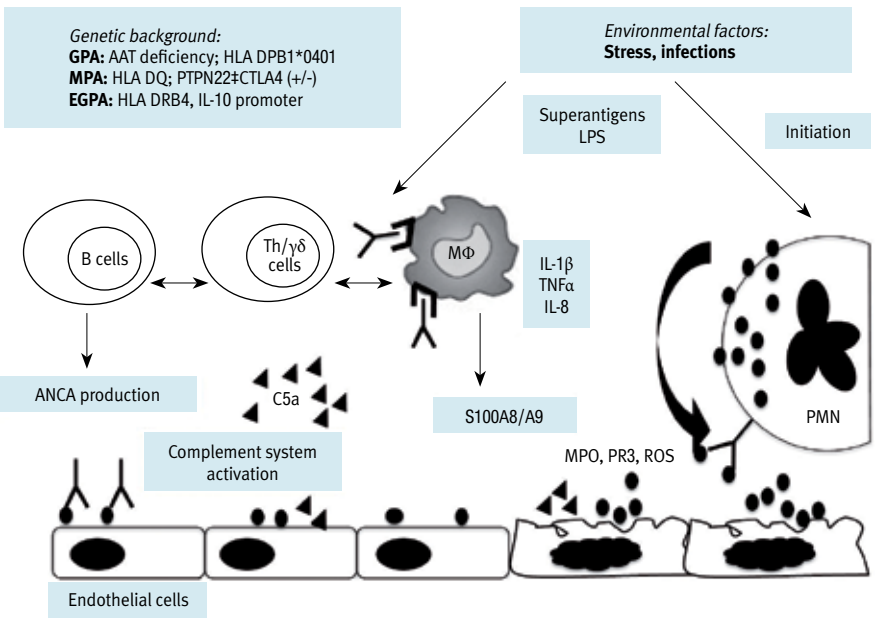
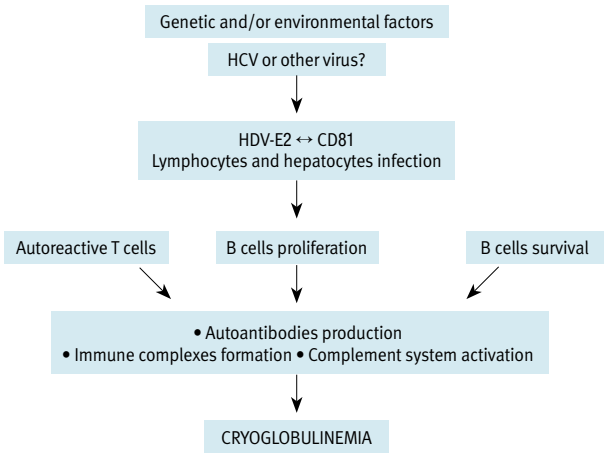


Figure 2. Pathogenic mechanisms of ANCA-associated vasculitis. Proposed model for anti-neutrophil cytoplasmic autoantibody (ANCA)-mediated vascular inflammation through alternative pathway complement activation. Neutrophils are primed by cytokines to express ANCA antigens (myeloperoxidase and proteinase-3) at the cell surface and then adhere to susceptible endothelium, and ANCA antibodies interact with the ANCA antigens, resulting in neutrophil activation. The ANCA-activated neutrophils release factors (properdin, factor B, proteases, ROS and MPO) that can directly damage the endothelium but also activate the alternative complement pathway with the generation of the powerful neutrophil chemoattractant C5a. This complement activation amplifies neutrophil influx and activation eventually culminating in the severe necrotizing inflammation of the vessel wall

ANCA = anti-neutrophil cytoplasmic autoantibody, AAT = alpha-1 anti-trypsin, PTPN22 = protein tyrosine phosphatase non-receptor type 22, CTLA4 = cytotoxic T lymphocyte antigen 4, LPS = lipopolysaccharide, B = B cells, Th = T helper, MΦ = monocytes/macrophages, IL-1β = interleukine 1-beta, TNFα = tumor necrosis factor-alpha, PMN = polymorphonuclear cells, MPO= myeloperoxidase, PR3 = proteinase 3, ROS = oxygen radicals

Figure 3. Pathogenesis of essential mixed cryoglobulinemia (ECM). In a genetically predisposed patient, a known antigenic stimulus (e.g., HCV) or unknown stimuli act on immune system cells. HCV is the major pathogenetic factor involved in EMC. It can stimulate the immune system as lymphotropic virus or as B cell activator. The result is a polyclonal activation of B cells and the production of autoantibodies and immune complexes. Those classically precipitate at low temperatures and are called cryoprecipitates. The cause of the precipitation could be structural modification of immunoglobulin variable light and heavy chains and a reduction in sialic acid or galactose in the constant fragment (Fc). HCV-E2 envelope protein can bind the CD81 expressed on B cells and hepatocytes. Interaction between CD81 and HCV-E2 increases the frequency of VDJ rearrangement and bcl-2 activation, with inhibition of B cell apoptosis, increased survival and autoantibody production. IC deposition as well as complement system activation leads to wall vessel damage. The histological outcome is a leukocytoclastic vasculitis [16,17]



Monoclonal CG are usually associated with hematological disorders, whereas mixed CG are found in many infectious and systemic disorders. The classical pathway of the complement system is usually activated in both essential and secondary cryoglobulinemia. Decreased C4 and C2 levels are observed together with slightly altered C3 levels in the disease course. Late complement components are insignificantly affected, although modest elevations have been reported. Diminished serum levels of complement components may reflect ongoing consumption by CG-containing IC [4]. Cryoglobulinemic vasculitis can be characterized by palpable purpura, arthritis, weakness, neuropathy and glomerulonephritis [18,19]. Although the presence of glomerulonephritis is associated with an overall poor prognosis, progression to end-stage renal failure is uncommon. Besides the detection of serum cryoglobulin itself, low C4 is often proposed as a serologic criterion for the diagnosis and classification of mixed cryoglobulinemia and may provide surrogate evidence of the presence of cryoglobulinemia. Moreover, HCV-mixed cryoglobulinemic patients who respond to treatment show a decrease in serum cryoglobulin levels and an increase in C4 serum levels [20].

URTICARIAL VASCULITIS

Urticarial vasculitis (UV) is a pathologic entity characterized by recurrent episodes of urticaria, with the histopathologic features of leukocytoclastic vasculitis, mainly involving capillaries and venules. UV may be idiopathic or associated with chronic diseases such as infections, hematologic diseases, connective tissue diseases, particularly systemic lupus erythematosus (SLE) and Sjögren's syndrome, and malignancy. Differing from urticaria, UV lesions last longer than 24 hours and may leave residual hyperpigmentation [21]. UV is an immune complex-mediated disease. Circulating antigen-antibody complexes initially form in the blood and then deposit in the vessel walls. Complement is activated through the classical pathway and C3a and C5a are generated. Based on the level of complement activation and consumption, several syndromes are described that differ only in severity and prognosis [22]. Normocomplementemic urticarial vasculitis (NUV) is a mild disorder with prevalent cutaneous involvement and normal serum complement levels. Conversely, hypocomplementemic urticarial vasculitis (HUV) is a multi-organ disease with possible gastrointestinal, musculoskeletal, renal, pulmonary and ophthalmologic involvement, and low level of serum complement proteins. The antigen involved in immune complex formation may be autologous (self-antigen) or exogenous (infective agent, drug). IgG autoantibodies to the collagen-like region of C1q in serum from HUV patients have been described frequently. These autoantibodies may account for the lowering of serum C1q in this syndrome and can be found in patients with other diseases, especially autoimmune conditions. In particular, anti-C1q has been detected in SLE (61%), rheumatoid arthritis (20%), scleroderma (15%), Sjögren's syndrome (15%), mixed connective tissue disease (15%), and even in chronic HCV infection (38%) [22]. Because of the presence of these autoantibodies in a large percentage of patients with both UV and SLE, some authors have hypothesized that these diseases could represent different expressions of the same autoimmune disorder. In SLE patients, anti-C1q levels correlate with the severity of skin and renal involvement. In UV, their pathogenic significance is not clearly elucidated but seems to be associated even with lung disease [23]. The diagnosis of UV is suggested by a typical clinical presentation and supporting laboratory tests (low levels of C3, C4 and C1q, presence of anti-C1q antibodies, high erythrocyte sedimentation rate), but is always confirmed by skin biopsy.

OTHER SMALL VESSEL VASCULITIDES

IgA vasculitis (IgAV) and IgA nephropathy (IgAN) are currently considered related diseases. Both diseases show similar

histological patterns and IgA abnormalities. The common clinical feature of IgAN is an indolent progressive disease with slowly increasing proteinuria and loss of renal function associated with episodes of macroscopic hematuria in half the patients. In the majority of patients, Henoch-Schönlein purpura nephritis (HSPN) is characterized by acute onset followed by full recovery [24]. The activation of the complement pathway is likely to be involved in the pathophysiology of glomerular lesions. Glomerular deposition of MBL, L-ficolin, MASP and C4d are observed in the vast majority of patients with HSPN and IgAN. These findings, together with the absence of C1q, are supportive of the predominant activation of the complement system by the lectin pathways as a pathophysiologic mechanism. The deposition of complement fragments derived from the activation of the lectin pathway has been shown to be associated with a higher degree of proteinuria and hematuria as well as with more severe histological lesions in both HSPN and IgAN patients [24,25]. These findings emphasize the need for further studies to assess the potential significance of measuring blood and urinary complement activation products and MAC to evaluate disease activity and potential therapeutic targets.

TREATMENT OF SMALL AND MEDIUM VESSEL VASCULITIDES

The treatment of vasculitides includes three phases: induction of remission, maintenance, and treatment of relapse. Treatment strategies for main small and medium vessel vasculitides are summarized in Table 1. Remission should be induced rapidly, balancing potential target organ damage against drug toxicity. Maintenance with immunosuppression should limit the amount of corticosteroid use and prevent relapse. Concomitant medication is used to treat or prevent adverse events from immunosuppressive treatment.

A combination of intravenous or oral cyclophosphamide (CYC) and glucocorticoids is recommended for inducing remission of generalized primary small and medium vessel vasculitis [6]. EULAR recommends that patients with ANCA-associated vasculitis be categorized according to different levels of severity to assist in treatment decisions [6]. In particular, patients with different levels of disease severity respond to different treatment protocols. The severity and extent of the disease classify patients into five groups: localized, early systemic, generalized, severe, and refractory. A combination of oral or parenteral methotrexate (MTX) and glucocorticoid can be used as a less toxic alternative to CYC for the induction of remission in non-organ-threatening or non-life-threatening ANCA-associated vasculitis [26]. Remission maintenance therapy consists of a combination of low dose glucocorticoid therapy with one of the following: azathioprine (AZA), leflunomide (LEF), or MTX, which were selected on the basis of randomized controlled trials [27]. In fact, the toxicity of long-term CYC makes it an unattractive option for this purpose. Remission maintenance therapy should be continued for at least 18–24 months as early cessation of therapy is associated with an increased risk of relapse [27].

Table 1. Management of ANCA-associated vasculitides, cryoglobulinemic vasculitis and urticarial vasculitis

Disease	Disease stage	Treatment
ANCA-associated vasculitides	Induction of remission	
	Localized	Co-trimoxazole for GPA
	Early systemic	MTX+GC
	Generalized	CYC+GC or RTX+GC
	Severe	As generalized + PE
	Refractory	IVIG, RTX, IFX, ATG, MMF, 15-deoxyspergualin
	Maintenance of remission	AZA or MTX or LEF or MMF + GC
Urticarial vasculitis	Cutaneous	Antihistamines, colchicine, dapsone, hydroxychloroquine, indomethacin, GC
	Extracutaneous or chronic cutaneous	GC
	Severe systemic or chronic GC resistant	AZA, CYC, CYA, MMF
Cryoglobulinemic vasculitis	Asymptomatic	Monitoring
	Mild-moderate	Low-medium dose GC ± LAC ± other symptomatic drugs
	Moderate-severe	Peg-IFN+Riba (in HCV patients) Low-medium dose GC
	Severe-rapidly progressive	CYC (or RTX) + GC + PE (± antiviral agents)

Therapeutic strategy should be established on the basis of the activity/severity of diseases and adjusted for the single patient

GPA = granulomatosis with polyangiitis, GC = glucocorticoids, CYC = cyclophosphamide, CYA = cyclosporine A, MTX = methotrexate, RTX = rituximab, PE = plasma exchange, IVIG = intravenous immunoglobulin, IFX = infliximab, ATG = anti-thymocyte globulin, MMF = mycophenolate mofetil, AZA = azathioprine, LEF = leflunomide, LAC = low antigen content diet, Peg-IFN = pegylated interferon, Riba = ribavirin

Alternative immunomodulatory therapy choices should be considered for patients who do not achieve remission, or relapse, on maximal doses of standard therapy. Treatment options in refractory disease include rituximab (RTX) and TNFa antagonists as well as intravenous immunoglobulins (IVIG), deoxyspergualin and anti-thymocyte globulin (ATG) [28,29]. In particular, RTX has emerged as an alternative for CYC in the remission induction of patients with generalized and severe disease [30].

Plasma exchange is reserved for selected patients with rapidly progressive severe renal disease in order to improve renal survival; it proved superior to methylprednisolone pulses in a controlled trial [31].

Treatment of cryoglobulinemic vasculitis should be established on the basis of the activity/severity of disease and adjusted for the individual patient. In the presence of active chronic hepatitis, eradicating the HCV infection should be attempted; severe, rapidly progressive disease must be treated with steroids and immunosuppressive agents, as in other systemic vasculitides. In HCV patients with acute and severe manifestations, some authors suggest combined or sequential therapy with RTX and antiviral agents [32].

Patients with urticarial vasculitis usually require antihistamines for the symptomatic relief of the pruritus. Systemic glucocorticoids are the mainstay treatment at the initial dose of 0.5–1.0 mg/kg per day. Indomethacin, colchicine, dapsone and hydroxychloroquine have been shown to be effective and to minimize side effects due to steroids. For severe or refractory HUVS, high doses of glucocorticoids may be needed, associated or not with other agents such as AZA, CYC, mycophenolate mofetil (MMF), cyclosporine A (CYA), and MTX. Plasma exchange has also been used [33]. The principles of treatment for UV and cryoglobulinemia are presented in Table 1.

Treatment of IgAV needs to balance the risk of chronic kidney disease (CKD) versus the risk and cost of the treatment. In the case of minimal renal symptoms such as microhematuria, short duration macroscopic hematuria or mild proteinuria, patients may not need treatment because of the low CKD risk. In the case of nephritic syndrome or nephrotic proteinuria, even without clinical nephrotic syndrome, treatment with glucocorticoids might be recommended [24]. The addition of immunosuppressive drugs might be considered when improvement is delayed or in situations of higher risk, even if results from randomized clinical trials with CYC were not encouraging. Plasma exchange should be considered promptly in patients in whom steroids and immunosuppressive drugs are not effective, or even initially when nephritic and nephrotic syndromes are associated with a high percentage of crescents [24].

THERAPIES TARGETING COMPLEMENT IN SMALL–MEDIUM VESSEL VASCULITIDES

A link between the complement system and tissue damage during ischemic, inflammatory and autoimmune diseases is increasingly recognized. This makes the complement system an attractive target for the treatment of a wide range of diseases, such as connective tissue diseases, glomerulonephritis, myocarditis, multiple sclerosis, type I diabetes mellitus, asthma, myocardial infarction, paroxysmal nocturnal hemoglobinuria, and vasculitides [34]. However, side effects potentially associated with the modulation of complement system in the long term must be considered. Prolonged systemic suppression may, for instance, increase the susceptibility to bacterial infections [35].

Several compounds interfering with the complement system cascade have been studied in experimental models for autoimmune diseases. The main therapeutic strategies are inhibition of complement activation components, inhibition of complement receptors, and inhibition of MAC [34].

Few studies on the use of anti-complement agents in vasculitic disorders have been conducted. Inhibitors of the C5a receptor (C5aR), a receptor distributed to a variety of immune cells including neutrophils, monocytes and dendritic cells, are in the early phases of investigation.

In 2012, Bekker et al. [36] presented a phase II clinical trial of CCX168 (a C5aR Inhibitor) in patients with a clinical diagnosis of granulomatosis with polyangiitis, microscopic polyangiitis or renal-limited vasculitis (CLEAR: C5aR inhibitor on Leukocytes Exploratory ANCA-associated Renal vasculitis). This multinational, randomized, double-blind, placebo-controlled clinical trial is being performed in 60 subjects in Europe. The primary objective of this clinical trial is to assess the safety and tolerability of CCX168. Secondary objectives include assessment of the feasibility of reducing or eliminating corticosteroids in the treatment of ANCA-associated renal vasculitis without the need for rescue corticosteroids, and evaluation of the effect of CCX168 treatment on renal function and ANCA disease. At the same meeting Dairaghi and colleagues [37] presented both animal and human phase I data on CCX168. This compound blocked C5aR activation following oral dosing in both humans and C5aR-humanized mice (hC5aR knockin mice). In the anti-MPO mouse model, CCX168 at a dose of 30 mg/kg achieved near-maximal inhibition of glomerulonephritis, with significant reduction of glomerular crescent formation and glomerular necrosis. The therapeutic benefit was associated with C5aR blockade on blood neutrophils ranging from 87 to 93%. In the phase I human clinical study, CCX168 was well tolerated, with excellent oral bioavailability and dose proportional increases in systemic exposure. Analysis of the human data revealed that 30 mg CCX168 twice daily provided excellent coverage of C5aR on human blood leukocytes. Further multicenter studies are needed to better define the long-term outcomes and safety profile of these new therapeutic agents. Only two complement modulators have been approved for use in humans to date: one is eculizumab, which binds to the complement protein C5, inhibiting its cleavage, and is indicated for the treatment of paroxysmal nocturnal hemoglobinuria [38]; the other is plasma-derived C1 esterase inhibitor, indicated for the treatment of hereditary angioedema [39].

Modulation of the complement system is one of the benefits associated with the use of high dose intravenous immunoglobulins (IVIg) in autoimmune conditions. The complement system-modulating effect exhibited by IVIg can be explained by several mechanisms. First, activated C3 and C4 may bind to immunoglobulin molecules, which then serve as scavengers, hence avoiding in situ deposition of these fragments [28]. Second, C1q may bind to immunoglobulin, leading to a deviation of C1 binding from its target to the IVIg. Third, IVIg

may enhance the inactivation of C3 in complex with immunoglobulins and thus down-regulate C3 convertase activity [39]. Finally, IVIg are able to evoke a mild and controlled activation of the complement system. This is not harmful and may reduce the pathological activation observed in the pathogenesis of autoimmune disease [28]. A broadly applicable anti-C therapeutic agent to treat acute and chronic conditions should be inexpensive, highly specific, have a long plasma half-life or be active orally, and able to block the pathological activation of the complement system while causing minimal disruption of the systemic complement function [40].

None of the currently available agents meet these requirements, but data derived from preclinical studies and initial clinical trials suggest that complement modulation could become an important therapeutic strategy in autoimmune conditions, including vasculitides, in the next decades. Based on the fact that AAV are infrequent conditions, further multicenter trials are needed to explore these potential new therapeutic targets.

CONCLUSIONS

Systemic vasculitides, in particular small-medium vessel vasculitides, are characterized by inflammation of blood vessel walls, IC deposition and activation of complement system. We have reviewed the contribution of complement system in the pathogenesis of these diseases. In particular, a close interaction has been demonstrated between complement system fragments, ANCA and systemic inflammation. The activation of complement system is crucial for the initiation, maintenance and perpetuation of the inflammatory process. Specific therapeutic regimens, including immunosuppressive drugs used to treat small vessel vasculitides significantly improves the prognosis and quality of life of affected patients but are known to be hampered by serious side effects and toxicity. According to the pathogenesis of systemic vasculitides, compounds interfering with the complement cascade are being explored as new therapeutic options in autoimmune diseases including ANCA-associated vasculitides and could represent a promising strategy in the near future.

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