ANCA associated vasculitis: The journey to complement-targeted therapies

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ABSTRACT

ANCA associated vasculitis is a serious, very often recurrent disease that despite the current standard treatment with high-dose glucocorticoids and either cyclophosphamide or rituximab, patients have a nine-fold increased mortality risk in the first year compared with healthy controls, attributed to infections, vasculitis activity, and renal disease.

During the last few years, novel findings have suggested that activation of the complement system, in particular the alternative complement system, has a significant role in ANCA associated vasculitis pathogenesis. Detection of several components of this system in the circulation and urine reflects disease activity, and thus may be useful for clinical prognosis and to set up personalised treatments. In fact, some components of the complement system, such as C5a, might be potential targets for therapy.

In this Review an update on clinical evidence for the role of complement activation in AAV is provided and subsequently we discuss potential therapeutic strategies that target complement components and open the way for clinical use of this target therapy in the near future.

1. Introduction

The spectrum of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) includes three clinical phenotypes: granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome). The availability of ANCA as a biomarker eases diagnostics and provides prognostic information. A cytoplasmic pattern (c-ANCA) and the target autoantigen proteinase 3 (PR3) are predominantly present in GPA (40–50% in localised GPA, 70–95% in generalised cases), while the perinuclear pattern (p-ANCA) and presence of myeloperoxidase (MPO) are observed in most MPA cases (70–95%) and to a lesser extent in EGPA (around 40%) (Millet et al., 2013; Greco et al., 2015). GWAS identified MHC and non-MHC associations with AAV and genetic associations better correlated with the ANCA serotype than with the clinical phenotype, supporting the concept that PR3 ANCA-and MPO ANCA-associated vasculitis are distinct autoimmune syndromes and should replace classification based on the clinical phenotype (Lyons et al., 2012).

AAV is a serious, very often recurrent disease that despite the current standard treatment with high-dose glucocorticoids and either cyclophosphamide or rituximab, patients have a nine-fold increased mortality risk in the first year compared with healthy controls, attributed to infections, vasculitis activity, and renal disease (Franssen et al., 2000). The prevalence of kidney involvement in AAV is 75–90%, and also impacts patients' quality of life and morbidity, particularly among those with end stage renal disease (ESRD) (Franssen et al., 2000). Moreover, a histological subgrouping of diagnostic renal biopsies has been proposed to aid in prognosis (Berden et al., 2010). Renal biopsy and baseline estimated glomerular filtration rate (eGFR) remain the most important outcome predictors available for ANCA associated renal vasculitis. The severity of proteinuria after the diagnosis is also a marker of the degree of injury and MPO-ANCA positive patients have a worse renal prognosis due to more severe chronic damage at the time of diagnosis (Quintana et al., 2014).

Currently used therapies contribute to more than half of the increased risk of mortality and represent an important cause of co-morbidities. Among them, glucocorticoids are associated with an increased infection risk and increase the risk to develop cardiovascular complications, particularly hypertension and diabetes mellitus (Little

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et al., 2010; Jayne, 2000; Koldingsnes and Nossent, 2002; Corral-Gudino et al., 2011; Takala et al., 2011; Mohammad and Segelmark, 2014).

The histopathological hallmark in the renal biopsy of patients with AAV is pauci-immune necrotising crescentic glomerulonephritis, which is characterised by no immunoglobulin and complement deposition in the glomeruli. In addition, hypocomplementemia is infrequent in patients with AAV (Franssen et al., 2000). These characteristics diverted the attention on a potential role of the complement system in the development of AAV over decades. However, gathering evidence during the last few years has suggested that activation of the complement system, in particular the alternative complement system, has a significant role in AAV pathogenesis. Detection of several components of this system in the circulation and urine reflect disease activity, and thus may be useful for clinical prognosis and to set up personalised treatments. In fact, some components of the complement system, such as C5a, might be potential targets for therapy.

In this Review an update on clinical evidence for the role of complement activation in AAV is provided and subsequently we discuss potential therapeutic strategies that target complement components and could improve patient and renal outcomes in this clinical context.

1.1. Complement and glomerular disease

The complement system and its regulatory proteins are components of the innate immune system with multiple roles in glomerulonephritis (GN) (Pickering and Cook, 2011; Puri and Quigg, 2007; Lesher and Song, 2010; Chen et al., 2010; Daha et al., 2011). The innate immune response involves immediate complement activation through the mannose binding lectin (MBL) or alternative pathways (Pickering and Cook, 2011; Puri and Quigg, 2007; Lesher and Song, 2010; Chen et al., 2010). Activation of the MBL pathway proceeds when MBL binds to mannose residues on pathogens and activates the serine proteases, MASP-1 and MASP-2, leading to activation of C4 and C2. The alternative pathway is activated spontaneously by hydrolysis of C3 and amplified by defects in complement regulation. Damaged cells and bacterial and viral proteins can also activate the alternative pathway beginning directly at C3. The same initiating event may activate more than one pathway (Daha et al., 2011).

Complement activation products are the main mediators of antibody-induced GN. Usually this involves C1q binding to Immunoglobulins that leads to classic pathway activation through C4 and C2; however, some immunoglobulins, depending on their level of glycosylation, can also bind MBL and induce GN. IgG subclasses 1 and 3 and IgM are classic complement pathway activators, whereas IgG 2 and 4, IgA, IgD, and IgE activate complement poorly (Chen et al., 2010; Daha et al., 2011).

All complement activation pathways proceed through cleavage of C3 and C5 leading to release of chemotactic factors such as C5a that attract inflammatory cells (neutrophils, macrophages, and platelets) when abutting the circulation as well as formation of the terminal membrane attack complex (C5b-9) (Pickering and Cook, 2011; Puri and Quigg, 2007; Lesher and Song, 2010).

Sublytic quantities of C5b-9 can insert into lipid bilayers of adjacent glomerular cell membranes, initiate several signaling pathways, and convert these cells to effector cells which may proliferate; release a variety of cytokines, growth factors, eicosanoids, oxidants, proteases, and other acute inflammatory mediators; as well as up-regulate production of matrix components that contribute to chronic scarring and sclerosis (Schroeder and Cavacini, 2010; Couser et al., 1985; Stevens et al., 2011). Complement activation products like C5a can also activate toll-like receptors (TLRs) (Stevens et al., 2011). Complement activation **in vivo** is tightly regulated by a number of circulating and cell-bound complement regulatory proteins, whose functions, mutations and deficiencies are also important in the development of several glomerular diseases. Abnormalities in serum complement profiles are in some cases

helpful in assessing the nature of the underlying disease and its activity, but significant complement-mediated injury may occur locally without alterations in circulating complement components (Pickering and Cook, 2011; Puri and Quigg, 2007).

1.2. Complement activation in the AAV pathogenesis

Until recently, the complement system was not studied in AAV because of its pauci-immune nature with absence of complement deposition in affected tissues and its rare association with hypocomplementemia (Jennette et al., 1989; Xing et al., 2009). The first evidence for a role of complement in AAV pathogenesis came from observations in animal studies. These models demonstrated that the alternative complement pathway was essential to the development of a necrotising crescentic GN (Xiao et al., 2007). Complement-depleted mice pretreated with cobra venom factor were protected from the development of GN, as evidenced after the induction of a pauci-immune crescentic GN by the administration of anti-MPO splenocytes to the mice. In these models, complement depletion prevented inflammation and crescent formation. Moreover, other studies clearly defined the contribution of the complement system to AAV pathogenesis. C5-knockout mice aiming to block activation of the terminal complement pathway were also protected as were mice lacking complement factor B, a critical regulatory component of the alternative complement pathway. By the contrary, C4-knockout mice developed the disease. In brief, these data confirm that the alternative pathway and the activation of complement C5 and the terminal complement pathway are critical to AAV pathogenesis.

Furthermore, supernatant from human neutrophils stimulated with either anti-MPO or PR3 IgG activated complement in normal human serum, prompting to the release of a complement-activating product by the ANCA-stimulated neutrophils (Xiao et al., 2007).

Additionally, pretreatment with a monoclonal antibody blocking C5 avoided the development of GN in mice and the lesion may be halted when given to mice after GN had been established (Huugen et al., 2007a). Further, in the mice model of ANCA-induced GN, lacking C5a receptor (C5aR) animal were protected from developing GN. Also, the role C5aR knockout improve the disease, while knockout of C5a-like receptor 2 (C5L2), resulted in more severe renal injury, suggesting that C5aR signaling enhance and C5L2 suppress the inflammatory pattern of lesion. By the contrary, C5b-9 end products had no role in the genesis of AVV (Xiao et al., 2007; Chen et al., 2017).

Animal data were interpreted with caution given the important differences between mice models and men, and consequently generated the reassessment of human data. In agreement with the results generated by animal models, this reevaluation confirmed that there were some clues that complement activation plays a role in human AAV (Chen et al., 2017). Despite that the intensity of the staining is not as bright as other observed in diverse GNs, renal biopsies of AAV patients do stain positive for some complement activation proteins (Xing et al., 2009).

Lately, investigation of renal biopsies of patients with ANCA-associated GN found an association between those biopsies showing presence of immune deposits and proteinuria (Scaglioni et al., 2017), as well as between alternative pathway proteins and crescent formation (Xing et al., 2009; Hilhorst et al., 2017). Other signs of complement activation in human AAV include increased levels of urinary alternative pathway activation products and presence of alternative pathway activation fragments in the serum (Gou et al., 2013a, b). Moreover, a study confirmed the presence of hypocomplementaemia in a small group of patients with worst overall and renal prognosis (Deshayes et al., 2018).

Less than 10% of patients with clinical and pathologic features of AAV with necrotizing GN are negative for ANCA using current clinical assays (Millet et al., 2013). It seems that Neutrophil activation and degranulation occurs in patients with ANCA-negative crescentic GN in

the absence of ANCA, and might be even more prominent than in their ANCA-positive counterparts (Wang et al., 2009). Finally, a proteomic analysis of renal tissues from AAV patients with ANCA-negative GN showed larger amounts of C3 and C9 deposition compared with ANCA-positive patients suggesting that ANCA-negative AAV was as a separate disease phenotype, promoted by a specific alteration in the activation of the alternative complement pathway (Sethi et al., 2017).

Since some years, the role of neutrophils in complement activation (both classical and alternative pathways) by expelling neutrophil extracellular traps (NETs) was well characterised (Leffler et al., 2012; Wang et al., 2015). In AAV, a study reported that neutrophils activated by MPO-ANCA released factors that had the capacity to activate the alternative complement pathway with the involvement of micro-particles (Camous et al., 2011) or NETs (Leffler et al., 2012; Wang et al., 2015; Camous et al., 2011; Schreiber et al., 2017).

From another point of view, a study showed that complement *factor H*, the main negative regulator of the alternative complement pathway, inhibits neutrophil activation by ANCA. Nonetheless, *factor H* from patients with active AAV was deficient in its ability to bind neutrophils and inhibit their activation suggesting that the complement system regulators may also play a protective role in neutrophil activation in AAV (Chen et al., 2018).

Even more, complement activation in AAV may not only result in neutrophil degranulation, but may also impact on the coagulation cascade. The effect of C5a on both neutrophils and endothelial cells to upregulate tissue factor and initiate the extrinsic pathway of coagulation is well known (Kambas et al., 2014). Platelets express C5a receptors and activated platelets may in turn push on complement and promote a vicious circle of neutrophils degranulation, coagulation, and lingering complement activation (Del Conde et al., 2005).

Fig. 1 depicts the proposed mechanism for involvement of complement activation in the pathogenesis of AAV.

1.3. Alternative complement pathway profile for disease stratification

In 2015, Manenti et al. reported, in a study that included 46 patients with AAV, that 35% of these individuals had decreased levels of C3 in serum, and this finding was associated with decreased renal survival

and the presence of renal thrombotic microangiopathy in the biopsy (Manenti et al., 2015). Recently, a study in 76 AAV patients reported that only 5% had hypocomplementaemia, however, this finding implied worst prognosis with lower overall and renal survival in this subset of individuals (Deshayes et al., 2018).

Moreover, the plasma level of properdin in patients with AAV in active stage was significantly lower than that in normal controls. The level of properdin inversely correlated with the proportion of crescents in renal specimens of AAV (Gou et al., 2013b).

Urine Levels of Bb, C3a, C5a and $C5b-9$ were higher in patients with active AAV than in patients in remission and levels of Bb correlated directly with serum creatinine, and inversely with the proportion of normal glomeruli in renal biopsies (Gou et al., 2013a; Yuan et al., 2012).

Complement deposits in renal tissue may also be a marker of disease severity. Their presence has been correlated with worst renal function and proteinuria at presentation; and a higher proportion of glomerular crescents and severe tubulointerstitial injury (Xing et al., 2009; Hilhorst et al., 2017; Chen et al., 2009). In fact, C3c deposition was found in renal biopsies and was associated with poorer renal function. $C5b-9$, C3d, and factor B, but not C4d, could be detected in active glomerular lesions and C3d and properdin staining was associated with the proportion of cellular crescents, confirming the role of C3d-staining as an independent risk factor for the development of ESRD (Villacorta et al., 2016).

Expression of the two C5a receptors, C5aR and C5L2, was mainly found on infiltrating neutrophils and macrophages. C5L2 was upregulated, whereas expression of C5aR was downregulated and correlated with serum creatinine levels at diagnosis and the extent of interstitial fibrosis (Yuan et al., 2012; Chen et al., 2009).

All these findings in plasma, urine and kidneys of AAV patients provide additional evidence that activation of the alternative complement pathway occurs in the development of AAV and may have a role in clinical stratification of disease severity.

1.4. Complement-targeted therapies in AVV

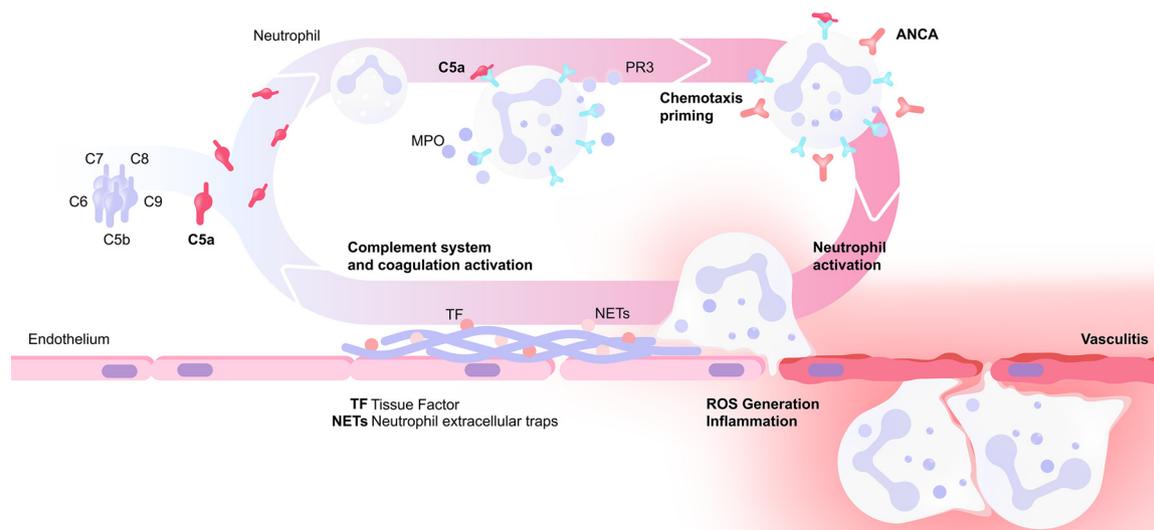Current therapeutic options for AAV are based on general immune-

Fig. 1. Characteristics of the pattern of injury in the current model of pathogenesis of ANCA-associated vasculitis. The interaction of anti-neutrophil cytoplasmic antibody (ANCA), neutrophils and complement activation plays a crucial role the amplification of the inflammatory process and constitutes an attractive therapeutic target. Priming of neutrophils by cytokines, such as C5a or tumour necrosis factor, leads to the translocation of ANCA antigens such as myeloperoxidase (MPO) or proteinase-3 (PR3) from the cytoplasm to the cell surface. ANCAs can further activate primed neutrophils to undergo respiratory burst and degranulation, and to release tissue factor (TF)-bearing microparticles and neutrophil extracellular traps (NETs). Neutrophil activation can lead endothelial cell injury, activation of the coagulation system, and activation of the alternative complement pathway via their cell membranes, microparticles and NETs. Activation of the alternative complement pathway and NETs in turn leads to the generation of C5a, which amplifies the inflammatory response through enhanced neutrophil recruitment and priming of neutrophils for ANCA-mediated activation.

suppression administrated as induction treatment with cyclophosphamide or rituximab and steroids. For maintenance treatment, azathioprine, methotrexate and rituximab are recommended. This standard of care has transformed these group of entities from a usually fatal disease into a chronic condition with co-morbidity and high relapse risk (Yates et al., 2016).

In this setting, finding new therapies to save steroid doses and prevent recurrence of disease are one of the main priorities. Given the background that complement is actively involved in pathogenesis, complement targeting therapies are very attractive option to solve this important clinical issue (Ricklin et al., 2018).

In recent years, drugs have been designed to target specifically one of the activation pathways of the complement cascade; it is possible to avoid blocking complement activation itself, by blocking the detection of activated complement fragments by cellular complement receptors instead. Using specific inhibitors that block one particular aspect of complement activation, the therapeutic result can be reached without affecting the other critical aspects of complement activation and innate immune response (Ricklin et al., 2018).

There are several classes of complement-inhibiting molecules in different phases of development, including therapeutic blocking antibodies, purified human proteins, recombinant proteins from pathogens, peptides or small interfering RNAs (Chen et al., 2017; Ricklin et al., 2018).

Only two types of these drugs are clinically available: the C5-blocking antibody eculizumab (Soliris®, Alexion Pharmaceuticals, Boston, Massachusetts, USA) and several C1-inhibitor (C1-INH) preparations (Cinryze®, Shire Pharmaceuticals, Dublin, Ireland; Berinert®, CSL Behring, King of Prussia, Pennsylvania, USA and Ruconest®, Pharming Group, Leiden, The Netherlands). The C1-INH preparations are mostly used for the treatment of angio-oedema (Cicardi et al., 2016).

Eculizumab has been available for clinical use for more that 10 years in the treatment of paroxysmal nocturnal haematuria (PNH) and atypical haemolytic uremic syndrome (aHUS), with very good outcomes and important information about its use and safety is available elsewhere (Wong and Kavanagh, 2015; Legendre et al., 2013; Lewis and Ram, 2014).

Due to differences between PNH and AAV pathogenesis, efforts for complement inhibition in AAV has been focused on inhibiting the signaling of the C5aR. Complement target therapy in AAV has been tested in animal models, blocking C5 activation prior to lesion induction could prevent MPO-ANCA-triggered vasculitis in mice and most of the effect of complement activation was mediated by C5aR1, the receptor for C5a (Huugen et al., 2007b; Schreiber et al., 2009).

These observations clearly indicate C5 and C5aR as possible therapeutic targets in experimental AAV using a small compound inhibitor of the C5a receptor with dose-dependent inhibition effect of MPO-ANCA induced GN (Xiao et al., 2014).

In line with these observations, there was no major role for the membrane attack complex (C5b-9) in the pathogenesis of AAV. Eculizumab avoids the cleavage of C5 but at the same time completely blocks membrane attack complex (MAC) formation in pathogens, potentially adding an undesirable and unnecessary risk of severe infections in the setting of AAV (Horiuchi and Tsukamoto, 2016).

1.5. CCX168: the oral C5aR blocker experience in ANCA associated vasculitis

As a consequence of these bench findings, clinical trials have been launched to test the safety and efficacy of an orally available human C5aR blocker, the small molecule CCX168 (Avacopan®, ChemoCentryx, Mountain View, California, USA). The phase I studies revealed a good safety profile, while producing more than 90% receptor blockade in inflammatory cells in the blood throughout the day (Bekker et al., 2016).

Next, the C5aR inhibitor on Leukocytes Exploratory ANCA-associated Renal Vasculitis (CLEAR) trial was performed using CCX168. In this randomised, double-blind, placebo-controlled phase II trial, CCX168 was orally administered to AAV patients. (Bekker et al., 2016) Three groups were compared: one receiving the standard treatment (cyclophosphamide/rituximab and high-dose prednisolone and placebo), one receiving CCX168 and prednisolone (cyclophosphamide/rituximab and low-dose prednisolone and 30 mg CCX168 twice daily) and the third group receiving CCX168 without prednisolone (cyclophosphamide/rituximab and no prednisolone and 30 mg CCX168 twice daily). At 12 weeks, it was observed that CCX168 was well tolerated with no unexpected adverse events. It was concluded that CCX168 was at least equally effective as the standard of care (Jayne et al., 2017). Following this trial, the Clinical ANCA Vasculitis Safety and Efficacy Study of Inhibitor of C5aR (CLASSIC) was performed. In this dose-ranging Phase II study of CCX168 which was added to standard of care, no safety concerns were reported and a dose-response effect of the treatment was established (Merkel et al., 2016). Currently, a Phase III Clinical Trial of CCX168 in AAV (ADVOCATE) is ongoing and will assess the proportion of patients achieving remission at 26 and 52 weeks (ADVOCATE trial, 2019).

2. Conclusions

Despite the use of the best available current therapies and achieving high levels of early clinical responses, ESRD caused by ANCA associated GN is an avoidable outcome yet, with rates approaching 40%. Major hurdles to management include the complex balance between toxicity associated with steroids and other immunosuppressive therapies and the risk of recurrence. The recent advances in the understanding of the role of complement in AAV pathogenesis clearly indicate C5 and C5aR as possible therapeutic targets in experimental AAV and open the way for clinical use of complement target therapy in the near future.

Declarations of interest

None.

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