



Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A Glimpse into The Future

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Article History	Abstract
Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 28 Oct 2023	<p>Background: A class of uncommon IgG4-related systemic diseases known as vasculitis caused by antineutrophil cytosolic antibodies (ANCA) is distinguished by the enlargement of small to large blood vessels. Objective: This review article offers an in-depth analysis of the most recent developments in ANCA-associated vasculitis, covering a range of topics from pathophysiology and diagnostics to treatment and long-term results. Methods: In this review we investigated the existing work on ANCA associated vasculitis by different sources such as Science Direct, Scopus, Pubmed, Web of Science, Google scholar and SciHub. Results: A number of diseases, including eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), and granulomatosis with polyangiitis (GPA), can have significant morbidity and mortality if they are not appropriately diagnosed and treated. Understanding the pathophysiology, clinical presentation, and curative options for ANCA-associated vasculitis have advanced significantly during the past ten years. The development of specific immunosuppressive medications has been largely responsible for the remarkable evolution in recent years in the treatment of ANCA-associated vasculitis. Conclusion: This review article has provided a detailed examination of the therapy for AAV, alternatives available, including induction and maintenance regimens, as well as the accompanying advantages and disadvantages. Additionally, the growing importance of biologic drugs like rituximab was examined, emphasizing its potential as supplements or replacements for traditional medical treatments.</p> <p>Keywords: Vasculitis, Antineutrophil Cytosolic Antibodies, Eosinophilic Granulomatosis with Polyangiitis, Microscopic Polyangiitis, Immunosuppressive Medications</p>
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1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a systemic autoimmune disease that mostly affects small and medium-sized blood vessels, including capillaries, venules, arterioles, and small arteries [1]. The connection between ANCA and vasculitis was initially discovered in brief research published in 1982 that described the clinical development of eight patients with segmental necrotizing glomerulonephritis. In the 1980s, the perinuclear and intracellular signals on secondary immunofluorescence (P-ANCA and C-ANCA), as well as the major particulars of myeloperoxidase and proteinase 3 (PR3), were recognized [2]. The three main clinicopathologic types of small vessel vasculitis associated with ANCA are eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss' disease), microscopic polyangiitis (MPA), and granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) [3]. There is a lack of knowledge regarding the circumstances

that led to the start of ANCA. By causing autoimmunity as a result of genetic variables, infectious agents, various specific medicines, environmental exposures, and other factors, certain factors contribute to the development of the disease [4]. Any body tissue can be impacted by systemic vasculitis, which can cause a variety of Injury patterns such lung capillaritis with bleeding, cutaneous leukocytoclastic angiitis producing purpura, and higher airway inflammation producing sinusitis are examples of injuries [5].

Types of ANCA vasculitis

There are three basic forms of ANCA associated vasculitis (AAV), and they are often identified by a combination of symptoms and histological examination results. Doctors frequently administer AAV treatments to patients based on their particular AAV subtype in addition to other disease-related factors. Microscopic polyangiitis (MPA): Depending on which areas are affected, MPA patients typically have a variety of symptoms, including kidney inflammation, skin lesions, and nerve damage. Fever and weight loss are frequent side effects. The most prevalent autoantibodies in these patients are MPO-ANCAs. Granulomatosis with polyangiitis (GPA): Individuals who have GPA may also suffer from blood vessel destruction in a variety of tissues, most frequently the lungs, kidneys, and upper respiratory system (nose, trachea, and ears). Granulomas, which are clumps of immune cells that develop in the vasculature, on the other hand, are the specific culprits for the inflammation. This type of ANCA vasculitis, formerly known as Wegener's granulomatosis, is usually linked to PR3-ANCAs.

Polyangiitis with eosinophilic granulomatosis (EGPA): EGPA usually only affects the lungs and digestive system, though it can also damage the heart and kidneys. Eosinophils, a different class of white blood cell of the immune system, make up the majority of the granulomas that are the cause of it. Before other vasculitis symptoms manifest, patients may endure asthma-like symptoms for several years [6].

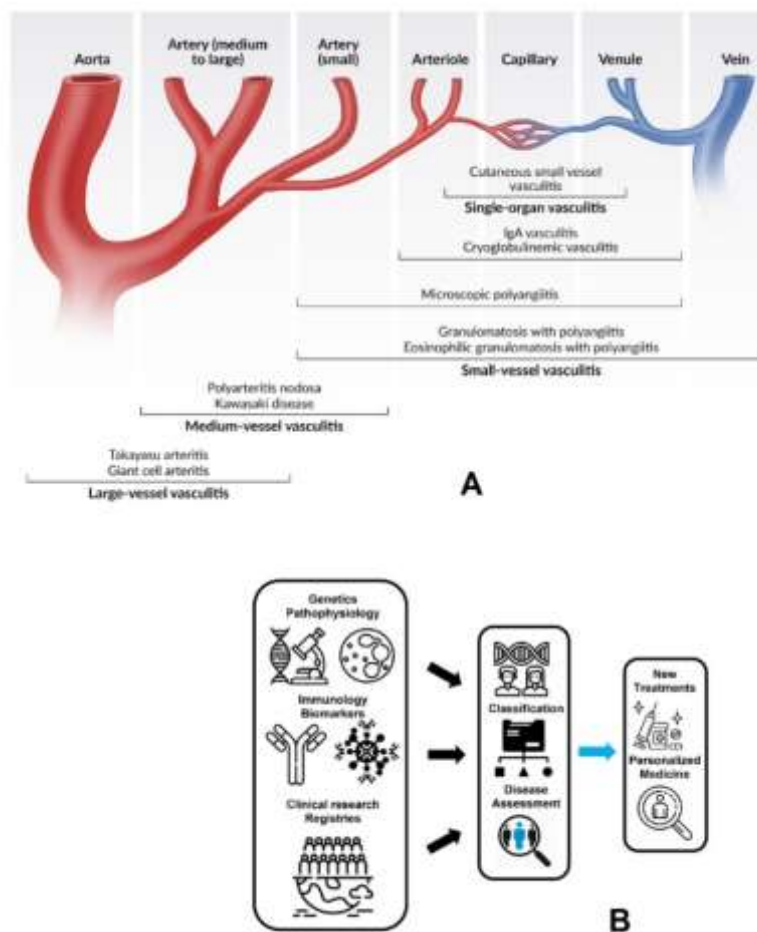


Figure 1: A) Types of ANCA associated vasculitis B) The conceptualization of vasculitis as a result of anti-neutrophil cytoplasmic antibody (ANCA)(Casal Moura M et al., 2022).

Epidemiology

GPA exhibits a cyclical pattern of occurrence, but not MPA. In contrast, MPA is more common than GPA in China and Japan. In AAV, familial instances are uncommon. While each illness-associated

allele carries only a small amount of risk, a number of genetic variables with relatively small effects work together to confer vulnerability to autoimmune disease and chronic inflammation. Notably, the HLA polymorphism influences regulatory T-cell (Treg) responses that are specific to the self-epitope, controlling the prevention or development of autoimmunity [7][8]. Geriatrics are at high risk for ANCA (Fig. 2).

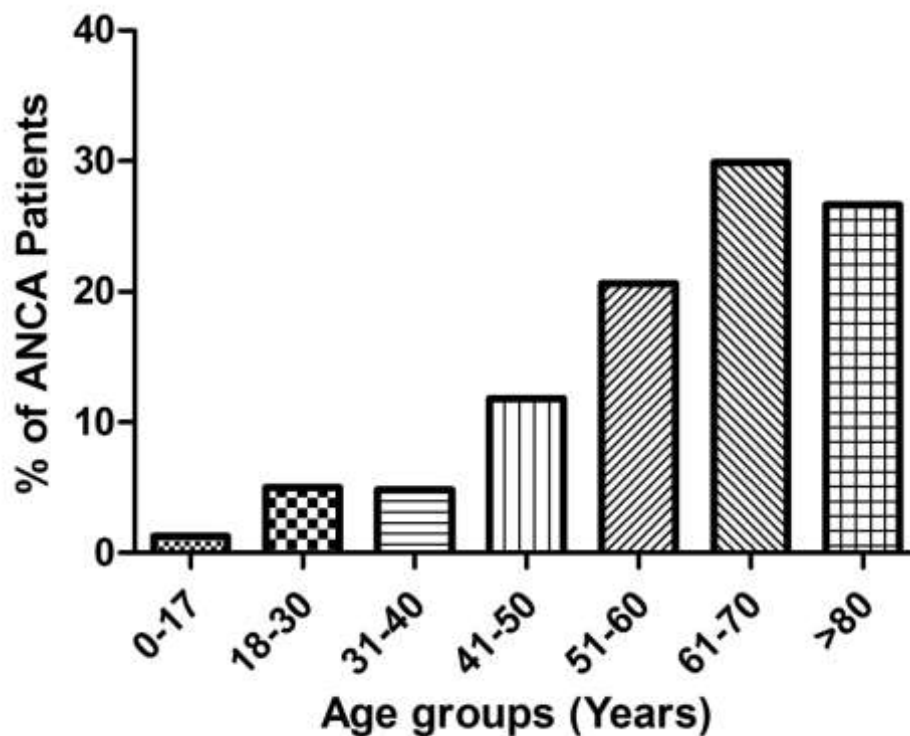


Figure 2: Anti-neutrophil cytoplasmic antibody associated vasculitis (ANCA) age distribution in 2015. The majority of ANCA patients were over the age of 50, with a peak age of 61-70 years (29.9%) [9].

Pathology

The idea that ANCAs actively participate in the pathophysiology of small vessel vasculitis is supported by a sizable body of research. Neutrophils are essential to AAV, and their reduction reduces the crescentic and pauci-immune necrotizing glomerulonephritis brought on by anti-MPO IgG. The ANCA-cytokine-sequence-theory can explain how ANCA production and small vessel vasculitis are related. First, immunogen infiltrates the infected body, dendritic cells grab the antigen, and T cells deliver it to activate macrophages and produce inflammatory cytokines that activate neutrophils, such as TNF and IL-1. Additionally, this process involves complement activation. In order to attach with the Fab of ANCA as well as the Fc region of the Fc receptors, which are found on neutrophils that were previously connected to ANCA, cytoplasmic MPO or PR3 is produced on the membrane shortly after neutrophil have been primed. Neutrophils that have been overactivated by ANCA generate vascular injury is brought on by NETs, matrix metalloproteinases, oxygen radicals, or lytic enzymes in them. CD4 lymphocytes or B cells that produce ANCAs receive MPO or PR3 that has been trapped on the membrane or in NETs by antigen-presenting cells. This pathophysiology is supported and maintained by numerous systems. [10].

Pathogenesis

1. Predisposing Factors: An increasing amount of research suggests that exposure to environmental stimuli mixed with a genetically defined background might disturb homeostasis and cause the creation of ANCA.
2. Genetic Associations: Despite the lack of evidence for transmission in AAV, genome-wide association investigations have revealed a unique genetic predisposition that is more closely correlated with more so than with clinical signs, ANCA specificity. Major Histocompatibility Group (MHC) type II expression polymorphisms, or SNPs, have been associated to AAV, with the presence of ANCA highly correlated with the HLA-DPB1*04 allele. MPO-AAV is connected to an SNP at the HLA-DQ gene, whereas PR3-AAV is connected to SNPs in the HLA-DP loci, specifically connected with the

HLA-DPB1*04 variant. The alpha-1-antitrypsin gene (SERPINA1) and the proteinase 3 gene (PRTN3) both have SNPs, and PR3-ANCA is connected to both of these genes [11].

3. Environmental Factors: AAV development may be influenced by environmental variables, according to mounting data. Latitude-dependent and seasonal triggers like UV radiation are among the geo-epidemiological triggers that have been found. Practitioners in the mining and construction industries showed a growing positive rate of ANCA in the 1990s. Silica is one of the compounds that is most frequently linked to the development of AAV. The rising frequency of AAV reported after three significant earthquakes in Asia provides additional evidence for the function of silica. Silica-induced apoptosis of macrophages and polymorphonuclear leukocytes, particularly MPO-ANCA positive MPA, may act as a trigger of AAV [12].

4. Infections: By priming molecular mimicry, neutrophils for ANCA-induced activation, and autoantigen exposure contained in neutrophil extracellular traps (NETs), infection promotes the loss of tolerance. Observational studies have suggested the involvement of infectious triggers in the pathogenesis of AAV, particularly the role of *Staphylococcus aureus* as a source of molecular mimicry in MPO-AAV or as a relapse trigger in GPA.

5. T- lymphocytes: It is thought that the broader adaptive immune system is crucial for the emergence of autoimmune reactions. In addition to assisting in the tissue damage effector pathways, vasculitis. There have been numerous described alterations in circulating T cell populations, with notably low levels of CD4+ T helper cells, a tendency towards effector memory T cells, different co-stimulatory molecule expression, and more T cells that are activated. It is still difficult to translate circulating T cell changes into an understanding of their effects within tissues. While enlarged CD4+ CD25+ T cell populations are primarily activated effector cells rather than Tregs, interest in T regulatory cells (Tregs) suggests that there is evidence for a numerical drop in Treg numbers and/or a functional insufficiency. There is evidence for increased activity of the T helper type 17 (Th17) subset with elevated serum IL-17 and IL-23 levels during acute disease, as well as increased autoantigen-specific IL-17-producing cells, suggesting that this fraction, which is dysfunctional in various autoimmune disease scenarios, may also be a factor when the disease is in remission as opposed to healthy controls. Mice lacking in IL-17A are protected from autoimmune anti-MPO glomerulonephritis in animal models. It has been convincingly shown by observations that a unique CD8+ T cell transcription signature can predict the chance of recurrence in ANCA vasculitis that events in the T cell compartment may affect the course of the disease [13].

6. B- lymphocyte: B lymphocytes play additional roles in the pathophysiology of AAV in addition to serving as the progenitors of ANCA-producing plasma cells. T cells receive antigens from B cells, which also produce cytokines that promote inflammation. They prime T cells for activation by stimulating their proliferation, differentiation, and polarisation through T cell activation. It has also been noticed that both disease activity and disease severity have been linked to the frequency of activated B cells. Additionally, tertiary lymphoid-like organs are generated in inflammation locations where autoantigen-specific B lymphocytes are present. All of these offer justification for the use of B cell-specific targeted treatments in AAV [14].

7. Complement system: The system of complementary therapies has previously been the subject of in-depth research. The Pasteur Institute's Bordet made the discovery of a serum component with bacteriolytic activity in 1895. There is mounting evidence that complement has a role in the pathogenesis of AAV. It has also been demonstrated that ANCA-stimulated neutrophils and NETs can both activate the complement system's alternative pathway, creating a positive feedback loop. In individuals with AAV, there is evidence of complement deposition at areas of tissue inflammation, such as C3d and factor B, and kidney deposition of Bb (a sign of activation of the alternative route), which is connected with the clinical severity of the disease. The complement pathway moves forward by converting complement proteins into their dynamic form, which contains activity of serine proteases, and by converting the cascading of downstream elements into their active state. The terms "lectin pathway," "classical pathway," and "alternative pathway", respectively, have been given to three complement activation cascades. Similar to how complement protein C3 is activated, the cascade's subsequent activation occurs after the C5 mechanism, despite the fact that the variables that cause each pathway have a different complement cascade and involve molecules. The C5 conversion enzyme splits C5 into C5a and C5b. Target cells are first attracted to C5b, which is followed by sequential binding to make the membrane assault complex (MAC), which pierces the lipid bilayer to create channels and kills target cells, combining C6, C7, C8, and C9. Numerous alternative complement pathways effects include

opsonization, phagocytosis primarily brought on via leukocyte chemotaxis and C3b primarily brought on by C5a [15].

2.2. Symptoms

AAV may show general symptoms of chronic inflammatory conditions (such as myalgia, polyarthralgia, weariness, weight loss, fever, and night sweats) or particular signs or symptoms of a chronic inflammatory disease participation of end organs. Almost everybody area can be impacted, although the lungs, kidneys, eyes, peripheral nerves, upper airways, and skeleton are the most often impacted systems. As a result, the following symptoms can present: ear pain, hearing, coughing, shortness of breath, wheezing, or hemoptysis (from lung involvement), and painful, red eyes (from scleritis). These symptoms are caused by upper airway involvement. Although many patients may not notice these symptoms, some individuals may experience numbness, tremors, or have trouble walking.. Peripheral neuropathy symptoms, such as foot drop or wrist drop, should be especially looked for during an examination [16]. 70% of individuals with EGPA and 90% of those with GPA had pulmonary involvement, compared to 50% of patients with MPA. Patients with glomerulonephritis frequently experience it together. From a brief infiltration, which is most frequently to cavitary nodules in the lungs, as observed in EGPA, which are seen in GPA, the severity of pulmonary involvement might vary. While hemorrhage can happen in all 3 disorders, GPA and EGPA patients may experience bronchial irritation. Patients may exhibit hemoptysis, breathlessness, and coughing. All EGPA patients also have asthma [17]. Renal involvement is a prominent characteristic of MPA. In MPA, pulmonary fibrosis and diffuse alveolar hemorrhage (DAH) have been more commonly accepted as the disease's initial symptoms [18]. The skin, intestines, and heart are among the other organs that are regularly impacted. Markers of inflammation are high, according to laboratory results. Compared to MPA and EGPA, which are related with myeloperoxidase (MPO)-specific ANCA, GPA is strongly connected to proteinase 3 (PR3)-specific ANCA. Relapse occurs more frequently in GPA. There are fewer cases with renal-limited AAV [19].

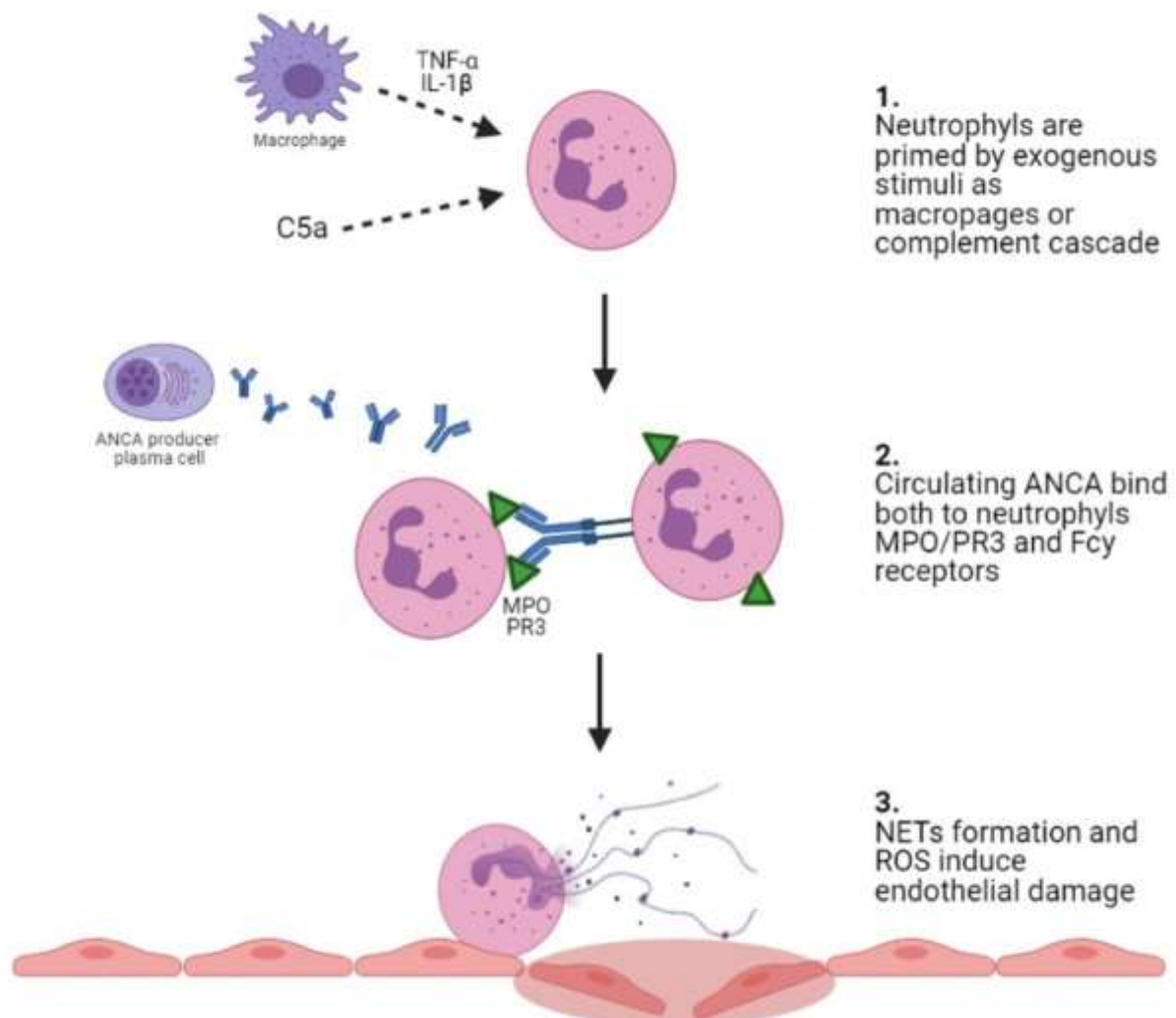


Figure 3. Etiopathogenesis of ANCA [20].

Complications

Either the disease itself or the therapy can result in complications. The aforementioned symptoms as well as organ involvement in the form of lungs, kidneys, and peripheral nerves are all complications of the illness. The patients also have a higher chance of developing oral ulcers, cardiovascular disease, myocardial infarction, hypertension, and cerebrovascular disease. Diabetes, osteoporosis, chemical cystitis, marrow failure, gonadal failure, and are among the side effects of treatment [21].

Diagnosis

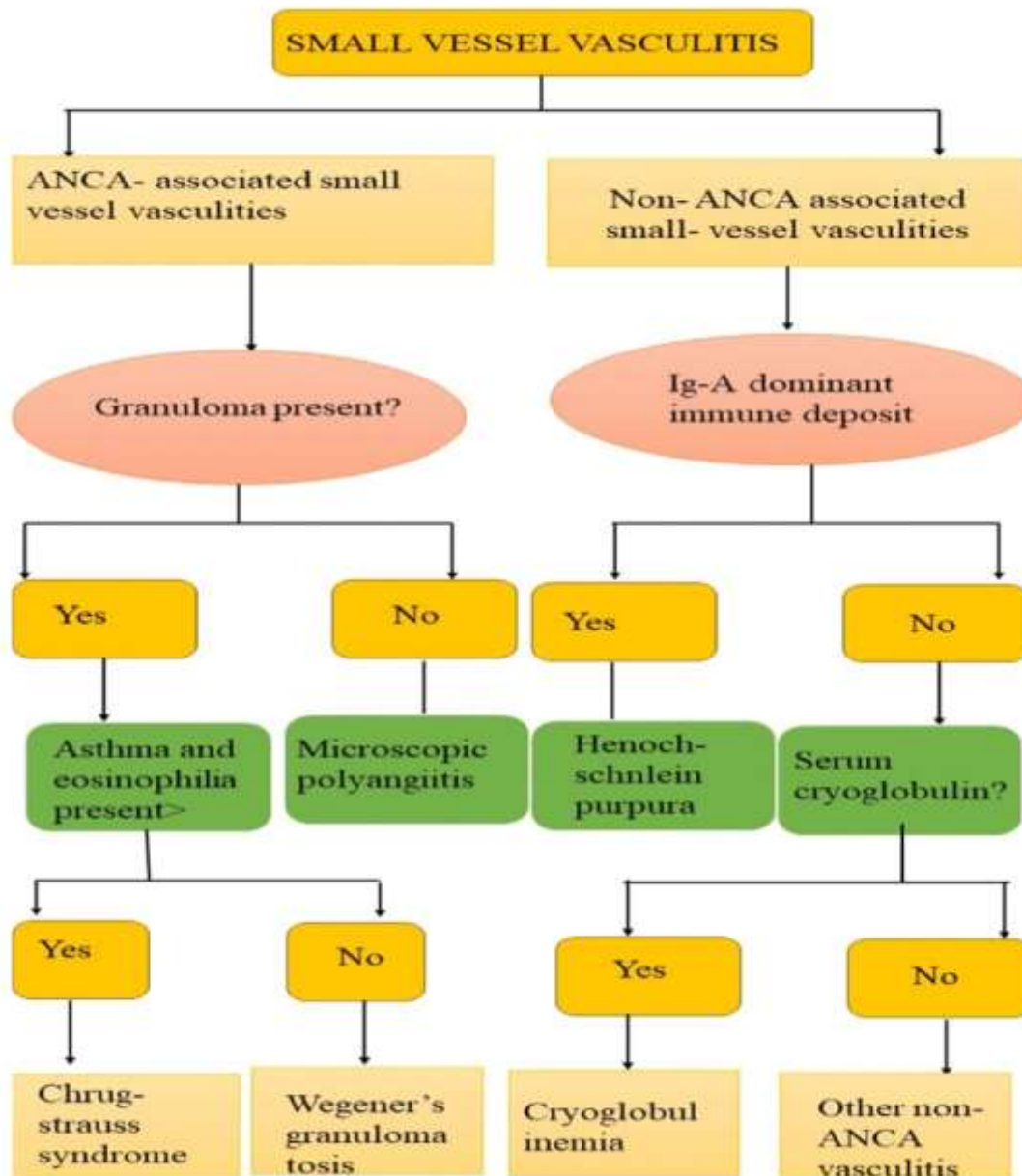


Figure 4: Diagnosis of small vessel vasculitis

Covid-19 and ANCA

About 20% of cases since COVID-19 first surfaced in December 2019 have been serious diseases that have presented with a range of clinical symptoms. During the diagnostic processes for these crucial patients, differential diagnosis of the various infectious and inflammatory disorders is quite important. The identification and management of AAV have been extensively studied at the time of the COVID-19 epidemic. COVID-19 has pulmonary involvement, and AAV may both occur at the same time, and COVID-19 alone may result in symptoms similar to those of AAV. As a result, it made the clinicians more cautious. In COVID-19 individuals, the diagnosis of new-onset AAV might be difficult because some of both diseases' signs and clinical manifestations are similar [22]. Similar pathways underlie COVID-19 and ANCA-associated vasculitis disease processes. As an example, both drugs cause NETs,

or extracellular neutrophil traps. NETs were found in infection induced by SARS-CoV-2, which cause severe injury to organ and high mortality rates, and are similar to ANCA-associated vascular inflammation, whereupon they become active, complement each other, and disrupt endothelial function. A decrease in C5aR1 receptor activity is a possibly beneficial therapeutic approach for ANCA-associated vasculitis, which is primarily triggered by the alternative complement pathway. Similar to COVID-19, which strongly depends on the C5a-C5aR1 transmitter axis, C5aR1 inhibition attenuated acute lung injury in a C5aR1 knock-in rat [23]. In addition to the occurrence of autoinflammatory/autoimmune phenomena in COVID-19 individuals, several COVID-19 vaccinations have infrequently related with a number of autoimmune disorders, including lupus nephritis and rheumatoid arthritis. The COVID-19 vaccination has also been linked to the induction of vasculitis. Following the COVID-19 vaccine, both the induction of vasculitis and a flare-up of an already-existing vasculitis have been reported. Rarely has it been shown that certain COVID-19 vaccinations, such as the Pfizer-BioNTech vaccine, can cause one kind of vasculitides, the AAV [24]. Due to known risk factors such old age and impaired renal function, people with AAV have the chance of developing severe COVID-19. Increased steroid dosages and ongoing induction therapy are both important indicators of risk, which raises concerns about the best stimulation strategy in an epidemic situation on a worldwide scale. Our results underline the significance of maintaining mitigation and shielding tactics, early COVID-19 detection, and a plan for rapid vaccination and booster shots for AAV patients [25].

Treatment

Rituximab

Rituximab (RTX), a monoclonal antibody that targets CD20, causes the depletion of peripheral B cells. The use of this in order to initiate and maintain remission in AAV has undergone successful testing and is approved [26]. For certain patient subgroups receiving AAV onset and maintenance therapy, RTX is essential. Following the application of CYC, the effectiveness of RTX in AAV was able to properly address the issues of conception maintenance and the higher risk of malignancy, considerably enhancing AAV survival. Relapse rates and hence the overall dose of corticosteroids can both be decreased with a maintenance treatment that contains RTX [27]. Rapid CD20-expressing B-cell precursor and mature B-cell depletion brought on by RTX can last for several months. The decrease is caused by cellular cytotoxicity and apoptosis that is antibody-dependent and complement-mediated. Eliminating malignant or auto-reactive B cells is the justification for utilizing RTX in autoimmune and malignant illnesses. Additionally, RTX can modify the T cell compartment by reducing antigen presentation to pathogenic auto-reactive T cells and by modifying the regulatory T cell compartment [28]. A strategy that is frequently used to keep patients in remission and avoid relapses is fixed-interval repeat-dose RTX infusions administered over a two-year period. Relapses do occur after a maintenance course of RTX, and additional dosing is considered when the risks of RTX-induced immunodeficiency and infection susceptibility must be evaluated against the benefits of relapse prevention [29]. Included are infections, late-onset neutropenia, hypogammaglobulinemia and infusion reactions as side effects of RTX treatment. Bacterial infections are the most prevalent infectious consequences. 79% of infections in people are brought on by them. people having pneumonia as a predominant illness who had RTX treatment for nephrological causes [30].

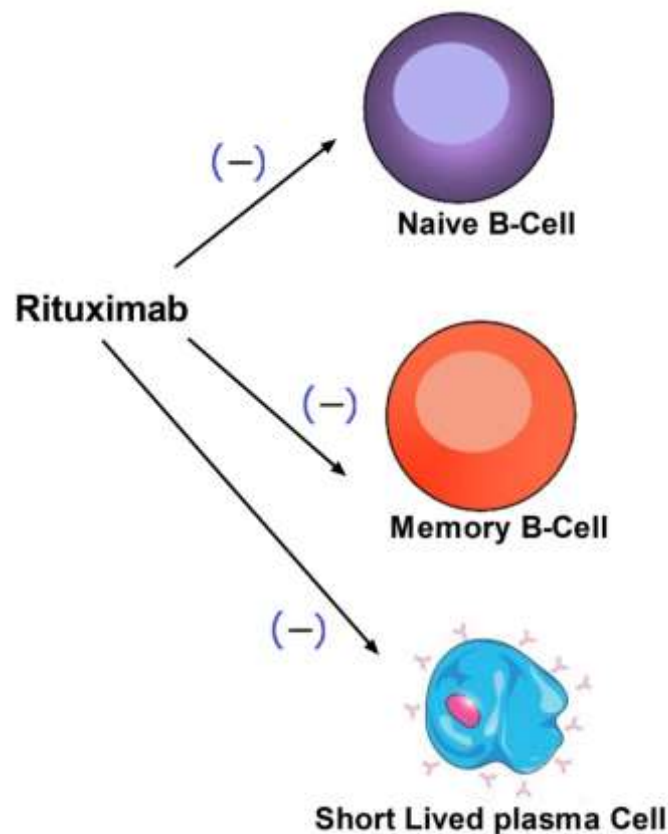


Fig. 5. RTX action on B- cells

Avacopan

In 2021 Avacopan is approved as a treatment for vasculitis caused by anti-neutrophil cytoplasmic antibody (ANCA) (AAV). In 2022, the European Medicines Agency (EMA) made a significant therapeutic progress. Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) has a novel, promising medication called Avacopan that has the potential to drastically lower steroid use [31,32]. Avacopan has been investigated as a possible medication for the treatment of AAV. It is an oral small molecule C5aR antagonist that inhibits the effects of C5a. Anti-myeloperoxidase (MPO) antibodies were the first to show that C5a receptor blockage might stop the development of glomerulonephritis in mouse models of AAV [33]. According to *in vitro* and *ex vivo* studies, avacopan suppresses the binding of C5a to C5aR, C5a-mediated motility, intracellular calcium mobilization, and integrin CD11b upregulation in human neutrophils. Avacopan, which cross-reacts with mouse C5a and is injected into mice expressing human C5aR, decreased anti-MPO antibody-induced NCGN in a dose-dependent manner. Avacopan pretreatment at a single dose also decreased neutrophil movement in response to an intraperitoneal thioglycollate injection in human C5aR knock-in mice. These findings suggest that avacopan's therapeutic effect is probably mediated by inhibiting C5a—C5aR interactions, which stop neutrophil activation and recruitment at inflammatory sites [34].

Avacopan, an oral medication taken twice daily, now has a significant role to play in remission induction regimens (when combined with background rituximab or cyclophosphamide) and should result in even shorter periods of glucocorticoids than were utilized in earlier trials. Avacopan, however, is not a substitute for glucocorticoids, according to the US Food and Drug Administration. The most efficient way to treat severe AAV is to combine avacopan with rituximab or cyclophosphamide. The main goal is to lower the amount of glucocorticoids needed to establish stable, long-lasting disease remission. Further research is necessary to determine its function in remission induction and maintenance in non-severe illness [35].

Corticosteroids

The best dosage and duration of glucocorticoids (GC) for treating ANCA vasculitis are still up for debate. Traditionally, intravenous (IV) methylprednisolone and 1 mg/kg per day oral prednisone have been used to treat ANCA vasculitis that poses a threat to life or vital organs [36]. Due to their general success in causing remission, GCs with Cyclophosphamide (CYC) have historically been regarded as the first-line treatment for AAV. Prior to the introduction of combination therapy, the mortality rate in

a year after diagnosis could reach 80%. High doses of GCs were typically administered initially to create the remission state and subsequently tapered down in order to achieve effective maintenance of the condition. The harmful effects of GCs, including developing diabetes, osteoporosis, a higher likelihood of diseases, glucose-induced psychosis, and gradual organ destruction, were measured using the glucocorticoid toxicity index [37]. There hasn't yet been a technique that enables clinicians to quantify the harmful consequences of GC treatment on an individual level, despite the fact that the effects of GC toxicity are widely known. Numerous investigations have shown a connection between GC toxicity and steroid intake. Steroids are still a key component of AAV treatment today, but more recent research has sought ways to limit steroid exposure [38]. This combo therapy has high remission rates of 80%–90% and was shown to lower mortality to 25% at 5 years. In addition to cyclophosphamide, therapy based on rituximab or methotrexate can also result in clinical remission. High-dose GC may increase treatment toxicity even though the combination of cytotoxic medicines with it greatly improves therapeutic efficacy [39].

Cyclophosphamide

Although GC is the foundation of AAV treatment, unless CYC became available as a combination therapy, mortality did not begin to drastically decline. The rate of remission has increased to 93% when CYC and GC therapy are combined. However, CYC has substantial treatment-related morbidity, much like GC, and there has been a push to decrease patient exposure. Some significant long-term negative effects linked to CYC include bleeding cystitis, genital disorder, tumors of the bladder, leukaemia, and lymphoproliferative carcinoma. [40]. Reduced ovarian reserve, ovarian failure, and male infertility are all linked to cyclophosphamide. For 3–6 months, cyclophosphamide is often given orally or as pulse therapy; after remission is attained, the cyclophosphamide is switched out for a less hazardous drug [41]. In order to avoid using steroids throughout maintenance therapy, a number of immunosuppressants are utilised, most notably azathioprine, methotrexate, and mycophenolate. It has been established that the alkylating agent CYC inhibits the development of B-cells, notably the formation of autoantibodies [42]. In organ-threatening autoimmune inflammatory rheumatic diseases (AIRDs), CYC is frequently used as a first line or rescue therapy. However, there is currently a movement towards the widespread use of Mycophenolate Mofetil (MMF) and Rituximab due to worries about CYC-related toxicities. With various proven induction procedures used in AIRDs, CYC has demonstrated efficacy. Compared to other agencies that are currently on the market, it is a more economical and cost-effective choice [43].

Plasma Exchange

An extracorporeal blood purification procedure of elimination of a patient's plasma from whole blood and replacement with either donated plasma or human albumin solution is known as therapy plasma exchange (TPE) or plasmapheresis. Pathogenic elements such as autoantibodies, immunological complexes, and lipoproteins are eliminated by TPE [44]. AAV has been managed with TPE for many years. Removing the antibodies should help, because it has been established that ANCA is directly harmful in numerous clinical and pre-clinical trials. Studies conducted in vitro have demonstrated that ANCA can bind to and activate both neutrophils and monocytes, causing the release of reactive oxygen species from the cells as well as cell attachment to endothelial cells in culture [45].

The effectiveness and safety of TPE for AAV have been examined in several randomized controlled trials (RCTs). Additionally, the results of the biggest RCT, the PEXIVAS research, were just released [46].

The largest randomized controlled trial ever conducted on ANCA-associated vasculitis, the Plasma Exchange and Glucocorticoids in Significant ANCA-associated Vasculitis trial, which was intended to assess the efficacy of TPE for people with significant kidney dysfunction or alveolar hemorrhage, failed to demonstrate improvements in the combined main results assess for death or ESKD in patients who received TPE [47].

There are two ways that TPE works:

1. The elimination of toxic substances from plasma (like IgG in the condition myasthenia gravis, IgM in Waldenström macroglobulinemia, or IgG and IgM iso-agglutinins before ABO incompatible organ donation). For the chemical to be efficiently eliminated by TPE, it is preferable that it be determined and evaluated to have a high molecular weight, a small distribution volume (particularly in plasma), an extended half- life, as well as a low turnover rate. It should be emphasized that the degree of material removal does not always correspond with the alleviation of clinical symptoms, unlike in myasthenia gravis..

2. The administration of significant quantities of insufficient plasma components, such as ADAMTS13 in thrombotic thrombocytopenic purpura (TTP). The fluid used to replace plasma should be made from or come from healthy donor plasma [48].

4.6. Intravenous Immunoglobulin

Over the past 20 years, high-dose intravenous immunoglobulin (IVIg) therapy has been successfully used to treat a number of dermatological autoimmune illnesses due to its immunomodulatory potential and low occurrence of severe side effects [49]. IVIG is a biological substance made of polyclonal antibodies that is made from the plasma of thousands of healthy people. For patients with primary immunodeficiency illness, IVIG was initially designed as an antibody replacement therapy to stave against dangerous infections [50]. IVIGs are plasma products made from the serum of thousands of healthy donors, as the quantity of donors increases the number of unique antibodies increases. IVIG products are used to control immunological reactivity in individuals with immune system problems because they have a high titer of antibodies against particular antigens. Polyclonal immunoglobulin G (IgG) makes up the majority of commercial IVIG preparations (>90%). Additionally, minor levels of other immunoglobulins, including IgM, IgA, and soluble molecules (such as the human leukocyte antigen, or HLA), are also present [51].

IVIg preparations have been found to contain anti-idiotypic antibodies against ANCA, which have been proven to suppress ANCA-induced neutrophil activation and cytokine release in vitro. It has been used IVIG successfully in AAV for patients with severe immunosuppression, relapsing diseases, and refractory diseases [52].

IVIg has been utilised successfully in the treatment of numerous autoimmune illnesses both as a single drug and as an adjuvant. In 1981, IVIg was used for the first time in a child with idiopathic thrombocytopenic purpura [53].

Table 1. Drugs and Mechanism of action

DRUG	MECHANISM
RITUXIMAB	B cell depletion is caused by a rituximab that attacks CD-20, a cell surface marker that is highly expressed on B cells.
AVACOPAN	Hinders the anaphylatoxin C5a and C5aR from interacting. Avacopan inhibits neutrophil activation and migration that is mediated by C5a.
CORTICOSTEROIDS	Mediate both genomic and non-genomic effects are the primary mechanisms of action. decreased synthesis of pro-inflammatory proteins is the result of membrane-bound GC receptors
CYCLOPHOSPHAMIDE	Alkylating agent CYC inhibits the development of B-cells, notably the formation of autoantibodies
PLASMA EXCHANGE	Ability to significantly reduce the number of circulating antibodies.
INTRAVENOUS IMMUNOGLOBULIN	Contain anti-idiotypic antibodies against ANCA, which have been proven to suppress ANCA-induced neutrophil activation and cytokine release in vitro. It has been used IVIG successfully in AAV for patients with severe immunosuppression, relapsing diseases, and refractory diseases.

4. Conclusion

If not adequately identified and treated, the complex category of autoimmune illness known as ANCA-associated vasculitis can have disastrous effects. Understanding the underlying causes, improving diagnostic procedures, and developing treatment plans have all advanced significantly over time. The range of available medicines has greatly changed, shifting from generalized immunosuppression to more specialized therapies. The development of biologic drugs like rituximab and belimumab has broadened the therapeutic toolkit by providing alternatives or complements to traditional immunosuppressive regimens. Remission of the disease, lowering the risk of relapses, and maintaining

organ function are now the main targets of treatment. Despite these developments, ANCA-associated vasculitis is still difficult to control over the long term. Relapse risk, potential organ involvement, and the effect on the quality of life of patients all continue to be major issues. The landscape of diagnosis and therapy has changed as a result of advancements in ANCA-associated vasculitis. To improve long-term results and raise the standard of living for those who will be impacted, however, considerable work remains to be done. We may work towards a future where ANCA-associated vasculitis is more successfully controlled, resulting in better patient outcomes and quality of life by expanding on the current knowledge and solving the remaining hurdles.

Abbreviations

ANCA	= Anti-neutrophil cytoplasmic antibody
AAV	= ANCA associated vasculitis
GPA	= Granulomatosis with polyangiitis
TNF	= Tumor Necrosis Factor
IL-1	= Interleukin-1
MPO	= Myeloperoxidase
PR3	= Proteinase-3
NETs	= Neutrophil extracellular traps
HLA	= Human Leukocyte antigen
CD20	= Cluster of differentiate 20
TPE	= Therapy plasma exchange
RCTs	= Several randomized controlled trials

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