Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/20102
DOI URL: http://dx.doi.org/10.21474/IJAR01/20102

RESEARCH ARTICLE

FROM GUIDELINES TO MISSED OPPORTUNITIES: A CRITICAL ANALYSIS OF ANCA VASCULITIS MANAGEMENT PRACTICES

Chaïmaa Zeroual, Merieme Benzakour, Mina Moudatir, Khadija Echchilali, Leila Barakat, Safaa Mourabit and Hassan El Kabli
Internal Medicine and Geriatrics, Ibn Rochd University Hospital Center, Casablanca, MAR.

Manuscript Info

Manuscript History
Received: 20 October 2024
Final Accepted: 23 November 2024
Published: December 2024

Key words:-
Vasculitis, ANCA, Management, Prognosis Tools, Activity Scores, Sequelae Evaluation

Abstract

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) represents a collection of rare autoimmune disorders that primarily target small blood vessels. This group includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA). The diagnosis of AAV is multifaceted, relying on a combination of clinical assessments, biological markers, radiological imaging, and histopathological evaluations.Although the revised Chapel Hill classification has refined disease definitions, the absence of ANCAs in some patients can complicate diagnosis. The management of AAV typically begins with an induction phase aimed at inducing remission. This phase often incorporates corticosteroids (CS) or Avacopan in conjunction with immunosuppressants such as Rituximab (RTX) or Cyclophosphamide (CYC). Following this initial treatment, patients generally transition to maintenance therapy. Despite significant advancements in the understanding and treatment of AAV, challenges persist regarding accurate prognosis and therapeutic management. To evaluate disease severity and inform treatment decisions, clinicians utilize tools such as the Five-Factor Score (FFS) and the Birmingham Vasculitis Activity Score (BVAS). However, these assessment instruments have inherent limitations and may not fully encapsulate the complexity of the disease. Recent epidemiological research has underscored geographic variability in the incidence of AAV and highlighted the role of ANCAs as crucial diagnostic and prognostic markers.Evaluating long-term sequelae using indices such as the Vasculitis Damage Index (VDI) is essential, especially given improved survival rates and an increasing focus on enhancing patients' quality of life.Current treatment strategies aim to minimize relapses and manage complications, including infections and metabolic disturbances; however, there is a pressing need for more personalized approaches.This review emphasizes the importance of developing more sophisticated prognostic tools and activity scores to improve clinical management of AAV. It also advocates for continued research to optimize treatment strategies and enhance outcomes for patients affected by these challenging conditions.

Corresponding Author:- Chaïmaa Zeroual
Address:- Internal Medicine and Geriatrics, Ibn Rochd University Hospital Center, Casablanca, MAR.

……

Introduction:-

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) encompasses a diverse array of aggressive diseases that wreak havoc on small-caliber blood vessels, including arterioles, capillaries, and venules. The primary manifestations of AAV are granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis; eosinophilic granulomatosis with polyangiitis (EGPA), formerly referred to as Churg-Strauss syndrome; and microscopic polyangiitis (MPA).

These formidable conditions are characterized by necrotizing inflammation that can lead to severe organ damage if not swiftly addressed [1]. The clinical landscape of AAV is marked by its potential to affect multiple organ systems, including the kidneys, lungs, skin, and nervous system, resulting in a spectrum of debilitating symptoms.Diagnosis hinges on a comprehensive evaluation that integrates clinical presentation, laboratory findings, and imaging studies.

While severity and activity scores can provide valuable insights, they are not without their shortcomings; these tools may either overestimate or underestimate the extent of damage associated with AAV. The Five-Factor Score (FFS), in particular, lacks the specificity and comprehensive criteria necessary for effective therapeutic decision-making, rendering it inadequate for guiding treatment selection. There is a pressing need to refine this score to enhance its ability to identify severe cases accurately.In parallel, the Birmingham Vasculitis Activity Score (BVAS) serves as a key tool for assessing disease activity across all forms of vasculitis, including AAV. Despite its thorough approach, combining BVAS with FFS may offer additional benefits in determining the necessity of incorporating immunosuppressants into corticosteroid therapy.Several evaluation scores exist for assessing long-term sequelae in AAV patients, with the Vasculitis Damage Index (VDI) being the most widely utilized [2].

Treatment protocols for AAV typically commence with an initial phase focused on achieving remission, followed by a sustained maintenance phase [3]. It is crucial to understand the indications, contraindications, and potential complications associated with any prescribed medications.

Our critical analysis aims to evaluate current diagnostic criteria, prognostic tools, and treatment strategies for AAV. We will highlight recent advancements in the field while identifying key areas for future research to enhance patient outcomes and optimize management strategies.

Epidemiology

AAV comprises a group of rare and complex autoimmune diseases, making their epidemiological study particularly challenging. The incidence of AAV in France mirrors that of Germany and the United Kingdom, with GPA being the most extensively studied subtype, occurring at nearly twice the rate of MPA in France [4]. In New Zealand, a comprehensive five-year study revealed a striking geographic disparity in AAV incidence, with significantly higher rates observed in the southern region compared to the north. This pattern reflects similar trends seen between northern and southern Europe [5].

Notably, Norwich, United Kingdom, reported the highest incidence rate of EGPA at an alarming 2.7 cases per million people [6]. Globally, AAV incidence exhibits variations between genders, generally showing a moderate male predominance. Over the past two to three decades, there has been a notable increase in AAV incidence with advancing age. This trend is likely attributable toheightened awareness of the disease and improved diagnostic capabilities leading to more frequent identification of cases in older populations [7]. The overall prevalence of AAV is estimated to be between 200 and 400 cases per million individuals, reflecting advancements in diagnostic testing and disease classification that have enhanced recognition and diagnosis. In the United States, recent data indicate an annual incidence of 3.3 cases per 100,000 people, significantly higher than earlier reports. This increase may be influenced by improved ANCA testing and greater clinical awareness [8].

While AAV remains a rare condition, its epidemiological landscape is evolving due to better diagnostic practices and increased awareness. Continued research is essential to fully understand the epidemiology of AAV and its implications for patient care.

Primary concept

Vasculitis, also known as angiitis, is a pathological condition characterized by the inflammation of blood vessels, which can include arteries, capillaries, and veins. This inflammatory process can affect various layers of the vessel wall—namely, the intima, media, and adventitia—resulting in cellular infiltration by neutrophil polynuclears (NPNs), eosinophilic polynuclears, lymphocytes, plasma cells, histiocytes, and giant cells. The consequences of such infiltration can lead to significant vascular damage and necrosis [9].

AAVs represent a group of rare, multisystem autoimmune diseases with an unclear etiology. These conditions are marked by inflammatory cell infiltration that results in necrotizing damage to blood vessels. ANCAs serve critical roles as both diagnostic and prognostic biomarkers in AAVs. Predominantly composed of immunoglobulin G, these autoantibodies target specific antigens located within the azurophilic granules of NPNs and the lysosomes of monocytes.

The classification of ANCAs is based on indirect immunofluorescence assays, yielding three primary types: PR3-ANCA (c-ANCA), which exhibits diffuse cytoplasmic staining and primarily reacts with proteinase 3 (PR3); MPO-ANCA (p-ANCA), which targets myeloperoxidase (MPO) and produces a characteristic perinuclear staining pattern; and atypical ANCA (x-ANCA), which recognizes other constituents of cytoplasmic granules distinct from PR3 or MPO. Notably, PR3-ANCA is found in approximately 75% of granulomatosis with polyangiitis (GPA) cases, while MPO-ANCA is present in about 60% of microscopic polyangiitis (MPA) cases [10]. The presence of x-ANCA is often observed in non-vasculitic conditions such as chronic inflammatory bowel diseases, certain malignancies, and various autoimmune disorders. Furthermore, both PR3-ANCA and MPO-ANCA can also be detected in chronic infections like endocarditis, tuberculosis, HIV, hepatitis C, and bartonellosis [11].

In instances where both PR3-ANCA and MPO-ANCA are identified concurrently in a single patient—a rare phenomenon—drug-induced vasculitis should be considered as a potential diagnosis. This underscores the complexity of AAVs and the necessity for thorough clinical evaluation to differentiate between primary vasculitides and secondary conditions that may mimic their presentation. Continued research into the pathophysiology and epidemiology of AAVs is essential for enhancing diagnostic accuracy and improving patient management strategies.

Prognostic tools

Five Factor Score (FFS)

The FFS is an essential tool utilized in guiding treatment decisions for patients diagnosed with AAV. The FFS comprises five clinical and biological criteria that correlate with the five-year mortality rate of affected individuals. Initially developed in 1996, the original FFS identified critical factors influencing overall survival specifically in patients with polyarteritis nodosa and EGPA. However, it did not encompass other forms of necrotizing vasculitides, which limited its applicability [12].

In 2011, the FFS underwent significant revisions to extend its relevance to additional systemic necrotizing vasculitides, particularly GPA and MPA. This update also involved the removal of certain criteria, specifically nervous system involvement and the measurement of 24-hour proteinuria, from the scoring system. According to the original 1996 criteria, the five-year mortality rate was recorded at 11.9% in patients without any prognostic factors. However, this rate escalated to 25.9% when one prognostic factor was present and exceeded 45.95% when two or more factors were identified [13,14].

The revised FFS introduced age over 65 years as a negative prognostic factor while designating ear, nose, and throat (ENT) involvement as protective against mortality, exhibiting a notably low relative risk of death. Based on the updated criteria from 2011, the five-year mortality rates stratified by FFS scores were found to be 9%, 21%, and 40% for scores of 0, 1, and 2, respectively 3. The revised FFS serves as a simplified scoring system aimed at enhancing prognostic evaluation and informing therapeutic decision-making [15].

Nonetheless, the FFS has inherent limitations; it considers only prognostic parameters at diagnosis without accounting for changes over time. Consequently, this may lead to an underestimation of disease severity since it primarily evaluates digestive, renal, cardiac, and ENT disorders while potentially overestimating severity in patients older than 65 years. Clinicians may encounter life-threatening visceral complications, such as rapidly progressing intra-alveolar hemorrhage; in such cases, an FFS score of 0 might suggest treatment with corticosteroids (CS) alone when aggressive immunosuppressive (IS) therapy is actually warranted for effective AAV management. Similarly,

in cases of GPA involving ENT structures, reliance on CS therapy alone is often inadequate due to frequent disease recurrences; therefore, repeated CS administration becomes necessary but is suboptimal as it increases risks for infectious and metabolic complications.

Incorporating IS agents into treatment regimens not only reduces reliance on CS but also aids in managing unpredictable relapses and flare-ups. Given that AAVs exhibit diverse life-threatening implications and functional consequences, employing a singular scoring system to unify their prognoses may be inappropriate. To enhance its utility, the revised FFS should be more specific and detailed and ideally integrated with an activity score that categorizes IS agents into "light" therapies such as azathioprine (AZA) or "aggressive" therapies like cyclophosphamide (CYC). This approach would facilitate more tailored therapeutic decisions based on individual patient profiles.

Antineutrophil cytoplasmic antibodies (ANCAs)

ANCAs are essential biomarkers in the management of AAV, providing critical insights into predicting responses to induction therapies and long-term patient prognosis. The two primary types of ANCAs—PR3-ANCA and MPO-ANCA—are associated with different clinical outcomes and treatment responses, influencing therapeutic decisions significantly.

Rituximab (RTX), a chimeric monoclonal antibody that targets CD20 on B cells, has been shown to be more effective than CYC in inducing remission in patients with PR3-ANCA type AAV. Studies indicate that RTX achieves higher remission rates compared to CYC, particularly in patients with relapsing disease [16]. In contrast, both RTX and CYC exhibit comparable effectiveness in the treatment of MPO-ANCA type AAV, suggesting that the choice of induction therapy may be less critical for this subgroup of patients [17].

Moreover, patients with PR3-ANCA are generally at a greater risk of relapse compared to those with MPO-ANCA. This increased propensity for relapse necessitates careful long-term monitoring and may warrant more aggressive maintenance therapy strategies for individuals with PR3-ANCA. The differential relapse rates highlight the importance of tailoring treatment approaches based on ANCA subtype to optimize patient outcomes [18].

In fact, ANCAs serve as crucial indicators for guiding treatment strategies in AAV. Understanding the distinct responses to RTX and CYC based on ANCA subtype not only enhances the likelihood of achieving remission but also informs clinicians about the potential need for ongoing therapeutic adjustments to prevent relapses. Continued research into the mechanisms underlying these differences will further refine treatment protocols and improve patient care in AAV.

Activity scores

They are essential tools for assessing the severity of AAV at diagnosis and during relapses. Among the various clinical and biological scoring systems available, the BVAS is the most widely utilized. Initially proposed in 1994, it has undergone revisions in 1997 and 2009, with the 2009 version being recognized as the most reliable and current iteration. This scoring system encompasses a comprehensive evaluation of nine organ systems to assess vasculitis activity and define treatment responses to various medications, including CYC, methotrexate, mycophenolate mofetil, intravenous immunoglobulins, and RTX.The BVAS version 3 comprises 56 distinct items, with scoring differentiated between recent lesions (less than 28 days old) and persistent ones. Higher BVAS scores indicate more active disease, with scores ranging from 25 to 35 reflecting very active disease that affects multiple organ systems. In 2001, the French Vasculitis Study Group introduced a specific adaptation of the BVAS tailored for GPA [12,19].

Despite its widespread use in assessing AAV, the BVAS has limitations; it cannot reliably distinguish between active vasculitis and progressive generalized infections due to overlapping clinical features such as fever, purpura, and headache. These infectious symptoms may arise secondary to the vasculitis itself, its treatment, or comorbid conditions. To enhance diagnostic accuracy, incorporating biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) into the BVAS could aid in differentiating between sepsis and significant disease activity. For instance, a high CRP level coupled with a negative PCT would suggest a disease flare-up. In contrast, elevated levels of both CRP and PCT typically indicate a generalized bacterial or fungal infection .

Additionally, monitoring ANCA levels may provide further insights; persistent ANCA positivity despite treatment can signal residual disease activity and an increased risk of relapse. An increase or return of ANCA positivity often

suggests an impending disease flare-up. Therefore, combining the FFS with the BVAS could enhance clinical decision-making regarding the necessity of adding IS therapy for managing AAV effectively.

While the BVAS remains a cornerstone in evaluating disease activity in AAV, its integration with additional biomarkers and scoring systems like FFS could significantly improve prognostic accuracy and treatment strategies.

Evaluation of Sequelae

The management of vasculitis has evolved significantly, with a growing emphasis on limiting sequelae due to improvements in overall survival rates among affected patients. A critical tool in this evaluation is the Short Form 36 (SF-36), a widely recognized instrument used to assess the impact of diseases on quality of life. Originating from the Medical Outcomes Study, the SF-36 aims to measure quality of life objectively and encompasses 36 questions that cover eight health domains [20].

In contrast, the VDI provides a more specific assessment tailored to vasculitis. While the BVAS records current disease activity, the VDI focuses on the long-term consequences of vasculitis and/or its treatment, as well as other comorbidities that may arise after diagnosis, regardless of their cause. Notably, this score can remain stable or increase over time; however, it does not decrease even if sequelae diminish months or years following remission [21].

It is straightforward to calculate, with each element contributing one point to the total score. Each evaluation incorporates all elements from previous assessments along with any new items identified, distinguishing it from the non-cumulative nature of the BVAS. The VDI specifically defines chronic damage and records any condition that has persisted for at least three months since the onset of vasculitis.Recent studies have highlighted the prognostic significance of this index. For instance, research indicates that early total VDI scores can independently predict all-cause mortality in patients with AAV. This underscores the importance of systematic damage assessment in this patient population [22].

Given VDI limitations, there is a growing consensus among experts that integrating this index with other assessment tools, such as the Combined Damage Assessment Index (CDA), could enhance its effectiveness. The CDA includes additional items that capture a broader range of damage types and provides a more nuanced view of patient outcomes [23]. Such integration could facilitate better management strategies by allowing clinicians to consider both disease activity and accumulated damage when making treatment decisions.

Treatment of AAV

Induction of Remission

The primary objective during the induction phase of treatment for AAV is to improve patient survival and achieve rapid remission. CS are typically initiated at a dose of 1 mg/kg/day, with a maximum daily dose not exceeding 60 to 80 mg. This initial treatment phase generally lasts for approximately four weeks. Depending on the severity of the disease, one or more boluses of methylprednisolone may be administered, typically at a dose range of 7.5 to 15 mg/kg/day, prior to the initiation of oral CS [24].

Avacopan's mechanism as an oral C5a receptor antagonist allows for targeted inhibition of inflammatory cell recruitment to the sites of vasculitis, potentially leading to better outcomes and fewer side effects associated with CS treatment.It represents a promising therapeutic option for patients with active AAV. Its favorable safety profile and ability to improve both clinical outcomes and quality of life underscore its potential as a first-line treatment.

In the Phase 3 ADVOCATE trial, avacopan demonstrated non-inferiority at six months and superiority at twelve months compared to high-dose CS combined with either CYC or RTX in patients with active AAV. Treatment with avacopan was well tolerated and associated with significant improvements in quality of life. Notably, among patients with severe renal involvement, those treated with avacopan experienced greater improvements in renal function compared to those receiving high-dose of CS [25].

In conjunction with CS or avacopan, CYC is often used as part of the induction regimen. CYC is administered as boluses every two weeks for the first month, specifically on days 1, 14, and 28, at a dose of 0.6 g/m². It is important to adjust the dosage based on the patient's renal function to optimize therapeutic efficacy and minimize toxicity [26].

RTX, an anti-CD20 monoclonal antibody, is now considered the standard treatment for AAV, particularly in cases of relapse or when patients do not respond adequately to CYC. RTX is also preferred for women of childbearing age due to its favorable safety profile during pregnancy [27]. In instances where RTX is contraindicated or in cases of refractory disease, obinutuzumab—another anti-CD20 agent—may serve as an effective alternative. Obinutuzumab has been shown to induce deeper and more prolonged depletion of B lymphocytes compared to RTX, potentially offering improved control over vasculitis activity [28].

Plasma exchange therapy can be beneficial for patients experiencing severe alveolar hemorrhage, persistent renal insufficiency despite treatment with CS combined with CYC or RTX, or rapidly progressive glomerulonephritis without a definitive diagnosis. This intervention may be particularly useful until results for antibodies against the glomerular basement membrane are available [29].

Maintenance of Remission

During the maintenance phase of treatment for AAV, the primary therapeutic objectives are to minimize the risk of relapse and to prevent complications associated with both the disease and its treatment. While the optimal duration of maintenance therapy has not yet been firmly established, current practices involve careful management of IS agents.

CS are typically utilized at a reduced dosage, maintained for a duration of 12 to 18 months. CYC may be administered at a dose of 0.7 g/m² every three weeks, usually consisting of six to eight boluses. However, CYC is generally not the preferred IS agent due to its association with an increased risk of long-term malignancies.

Alternatives such as AZA at a dose of 2 to 3 mg/kg/day or methotrexate at 0.3 mg/kg/week are frequently employed, as they demonstrate comparable tolerability and effectiveness in maintaining remission [30]. Mycophenolate mofetil (MMF) is another IS option during this phase; while it can effectively replace CYC, it is generally considered less effective than AZA in preventing relapses. Consequently, MMF is not typically used as a first-line treatment but remains a valuable alternative, particularly in patients with MPO-ANCA vasculitis [31].

RTX can also be utilized during the maintenance phase, as it has been shown to achieve remission without the need for additional immunosuppressive therapy. The recommended regimen involves administering RTX at a dose of either 500 mg or 1000 mg at fixed intervals every six months for up to two years following the completion of induction therapy. Despite its efficacy, the risk of relapse persists after discontinuation of RTX, underscoring the necessity for ongoing monitoring and follow-up care [32].

Contraindications for Corticosteroids(CS)and Immunosuppressive (IS) Therapy

When considering the use of CS and IS agents in treatment regimens, it is crucial to be aware of specific contraindications that may impact patient safety and treatment efficacy.

True contraindications to CS therapy are relatively rare but include severe progressive infections, glaucoma, cataracts, and certain psychiatric disorders. While diabetes is not an absolute contraindication, it is important to note that corticosteroids can temporarily exacerbate glycemic control, necessitating careful monitoring. Additionally, the use of CS should be approached with caution in patients with osteoporosis or severe hypertension, as these conditions can be aggravated by steroid treatment [33].

Certain vaccines are contraindicated during CS therapy. Patients should avoid live vaccines such as measles, mumps, rubella, tuberculosis, and varicella to prevent potential complications associated with weakened immune responses.

For IS therapies, absolute contraindications include serious progressive infections—whether viral, bacterial, parasitic, or fungal—as well as any live vaccines and specific neoplasms. These restrictions are critical to safeguarding patients from the heightened risk of infections and other adverse effects associated with immunosuppression.

In cases of hepatic and renal insufficiency, precautions must be taken when administering IS agents to mitigate potential complications. Furthermore, it is essential to discontinue IS therapy during pregnancy and breastfeeding to

protect both maternal and fetal health. However, AZA is an exception; it is considered safe for use during pregnancy [34].

Complications of AAV Treatment

AAV presents a range of complications, particularly following treatment with CS and IS agents. Understanding these complications is crucial for optimizing patient management and improving outcomes.

Infectious Complications

Infectious complications are common in patients receiving CS or IS therapy. These can include bacterial pneumonia, septicemia, viral infections, and opportunistic infections such as pneumocystosis, aspergillosis, and candidiasis. Effective anti-infective prophylaxis has been demonstrated in patients with GPA usingtrimethoprim-sulfamethoxazole (160 mg/800 mg) administered three times per week, particularly in those with leukopenia (CD4 <300/mm³) undergoing treatment with CYC [35].

Carcinogenic Risks

CYC and AZA are the IS agents most commonly associated with an increased risk of malignancy. CYC is known to cause hemorrhagic cystitis and bladder cancer due to the oncogenic effects of its metabolites, such as acrolein, on the bladder mucosa. Preventative measures include ensuring adequate fluid intake to dilute acrolein exposure and administering mesna to protect the bladder lining [35,36]. Long-term use of AZA in chronic inflammatory conditions has also been linked to an elevated risk of lymphoma [37].

Metabolic Complications

Prolonged or high-dose CS therapy can lead to significant metabolic complications, including dysregulation of glucose levels, lipid profiles, and blood pressure. These issues may necessitate the use of antihyperglycemic agents or insulin, lipid-lowering medications, and antihypertensive drugs. While strict dietary restrictions such as salt-free or sugar-free diets lack robust scientific validation, adequate daily intake of vitamin D (800 IU) and calcium (1 g) is recommended to support bone health. Patients are also encouraged to maintain a balanced diet and engage in regular physical activity to mitigate these risks [38].

Osteonecrosis and Osteoporosis

Osteonecrosis of the hip and humeral head is a frequent complication associated with extended CS therapy. Additionally, osteoporotic fractures may occur due to both CS use and menopause resulting from IS therapy. To prevent these complications, systematic supplementation with vitamin D and calcium is advised, along with anti-osteoporosis treatments such as bisphosphonates for patients on CS therapy at doses of 7.5 mg/day or higher for more than three months—especially in postmenopausal women and men over 50 years old [39].

Conclusion:-

The treatment landscape for AAV has seen remarkable advancements in recent years, with a strong emphasis on maintaining remission as a primary therapeutic objective. While prognostic tools such as FFS and activity indices like the BVAS play important roles in managing AAV, their practical contributions to patient care are still somewhat limited.To further enhance clinical outcomes and optimize management strategies, there is a pressing need for the development of new, more relevant scoring systems that can better reflect the complexities of AAV. By focusing on innovative approaches to assessment and treatment, we can improve our understanding of this challenging disease and ultimately provide more effective care for patients. The future of AAV management lies in our ability to refine these tools, ensuring they meet the evolving needs of both clinicians and patients alike.

References:-

[1] Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers 2020;6:71.
[2] Pagnoux C, Seror R, and Puéchal X. Systemic vasculitides: Classification criteria, activity score and pronostic score. Rheumatism Review Monographs 2010;77:121-7.
[3] Terrier B. Treatment of ANCA -associated vasculitides: Certainties and controversies. Nephrol Ther 2019;15(1):S7-S12.
[4] Berti A, Cornec D, Crowson CS, Specks U, Matteson EL. The Epidemiology of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis in Olmsted County, Minnesota: A Twenty-Year US Population-Based Study. Arthritis Rheumatol. 2017;69(12):2338-2350.

[5]Gibson A, Stamp LK, Chapman PT, O'Donnell JL. The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a Southern Hemisphere region. Rheumatology 2006;45(5) :624-8.
[6]Watts RA, Lane SE, Bentham G, Scott DGI. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. Arthritis Rheum. 2000;43(2):414-419.
[7] O'Donnell J, Stevanovic V, Frampton C, Stamp L, Chapman P. Wegener's granulomatosis in New Zealand: Evidence for a latitude-dependent incidence gradient. Internal Medicine Journal 2007; 37: 242-6.
[8] Rathmann J, Segelmark M, Englund M, Mohammad AJ. Stable incidence but increase in prevalence of ANCA-associated vasculitis in southern Sweden: a 23-year study. RMD Open. 2023;9(1):e002949.
[9] Savage CO, Harper L, Cockwell P, Adu D, Howie AJ. ABC of arterial and vascular disease: vasculitis. BMJ. 2000;320(7245):1325-8.
[10]Radice A & Sinico RA : Antineutrophil cytoplasmic antibodies (ANCA). Autoimmunity 2005; 38(1):93-103.
[11] Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13:683-692.
[12] Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Annals of the Rheumatic Diseases 2024;83:30-47.
[13] Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: A Prospective Study in 342 Patients. Medicine 1996;75(1):17-28.
[14] Guillevin L, Pagnoux C, Seror R, et al. The Five-Factor Score Revisited: Assessment of Prognoses of Systemic Necrotizing Vasculitides Based on the French Vasculitis Study Group (FVSG) Cohort. Medicine 2011, 90(1):19-27.
[15] Ahn SS, Lee SW. Management of antineutrophil cytoplasmic antibody-associated vasculitis: a review of recent guidelines. J Rheum Dis. 2023;30(2):72-87.
[16] Puéchal X, Iudici M, Perrodeau E et al. Rituximab vs Cyclophosphamide Induction Therapy for Patients With Granulomatosis With Polyangiitis. JAMA Netw Open. 2022;5(11):e2243799.
[17] Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA et al. European Vasculitis Study Group : Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211-20.
[18]Cornec D, Gall EL, Fervenza F, et al. ANCA-associated vasculitis — clinical utility of using ANCA specificity to classify patients. Nat Rev Rheumatol. 2016, 12:570-579.
[19] Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009;68(12):1827-32.
[20] Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473-83.
[21]Koo G, Ha JW, Ahn SS, Song JJ, Park YB, Lee SW. Earliest total vascular damage index scores independently predict all-cause mortality in patients with ANCA-associated vasculitis. Clin Exp Rheumatol. 2024;42(4):795-802.
[22] Bhamra K, Luqmani R. Damage Assessment in ANCA-Associated Vasculitis. Curr Rheumatol Rep. 2012;14:494-500.
[23] Suppiah R, Flossman O, Mukhtyar C, Alberici F, Baslund B, Brown D and al. Measurement of damage in systemic vasculitis: a comparison of the Vasculitis Damage Index with the Combined Damage Assessment Index. Ann Rheum Dis. 2011;70(1):80-5.
[24] Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Annals of the rheumatic diseases 2009;68:310-7.
[25] Tesar V, Hartinger JM, Hruskova Z. Avacopan as an add-on therapy for ANCA-associated vasculitis: a pharmacological overview. Expert Rev Clin Pharmacol. 2024;29:1-15.
[26] Schönermarck U, Gross W & de Groot K. Treatment of ANCA-associated vasculitis. Nat Rev Nephrol. 2013;10:25-36.
[27] Hassan RI, Gaffo AL. Rituximab in ANCA-Associated Vasculitis. Curr Rheumatol Rep. 2017;19:6.
[28] Amudala NA, Boukhlal S, Sheridan B, et al. Obinutuzumab as treatment for ANCA-associated vasculitis. Rheumatology 2022;61:3814-3817.
[29] Andreas Kronbichler, Jae Il Shin, Chia-Shi Wang, et al. Plasma exchange in ANCA-associated vasculitis: The proposition. Nephrology Dialysis Transplantation 2021;2:227-231.
[30] Pagnoux C, Mahr A, Hamidou M. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. New England Journal of Medicine 2008;359:2790-2803.
[31] Jones RB, Hiemstra TF, Ballarin J et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Annals of the Rheumatic Diseases 2019;78:399-405.
[32] Tieu J, Smith R, Basu N et al. Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines. Rheumatology 2020;59:24-32.

[33] Zoorob RJ, Cender D. A different look at corticosteroids. Am Fam Physician 1998;58:443-50.
[34] Hussain Y, Khan H. Immunosuppressive Drugs. Encyclopedia of Infection and Immunity 2022;8:726-40.
[35] Miller LJ, Chandler SW, Ippoliti CM. Treatment of Cyclophosphamide-Induced Hemorrhagic Cystitis with Prostaglandins. Annals of Pharmacotherapy 1994;28:590-594.
[36] Fairchild WV, Spence CR, Solomon HD, and al. The incidence of bladder cancer after cyclophosphamide therapy. The Journal of urology 1979;122:163-164.
[37] Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clinical Gastroenterology and Hepatology 2015;13:847-858.
[38] Dujoune CA & Azarnoff DL. Clinical complications of corticosteroid therapy: a selected review. Medical Clinics of North America 1973;57:1331-1342.
[39] Eastell R. Management of corticosteroid-induced osteoporosis. UK Consensus Group Meeting on Osteoporosis. Journal of Internal Medicine 1995;237:439-447.