A Descriptive Register of ANCA-Positive Vasculitis Patients with Kidney Involvement: A Portuguese Center Experience over 13 Years

Adriana Santos[1], Núria Paulo[1], Nídia Marques[1], Rafael Figueiredo[1], Ana Pinho[1], Edite Pereira[2], Eva Mariz[3], Ricardo Neto[1], Inês Ferreira[1]*

1. Nephrology Department, ULS São João, Porto, Portugal
2. Internal Medicine Department, ULS São João, Porto, Portugal
3. Rheumatology Department, ULS São João, Porto, Portugal

https://doi.org/10.71749/pkj.74

Abstract

Introduction: Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a necrotizing disease affecting small blood vessels, commonly involving the kidneys, and associated with high morbidity and mortality.

Methods: We conducted a descriptive cross-sectional study at Hospital de São João in Porto, including patients aged 18 or older with biopsy-proven kidney involvement from AAV, followed by a multidisciplinary team from December 2010 to June 2023. We analyzed demographic, clinical, and laboratory variables, kidney pathology findings, treatment regimens, and patient outcomes.

Results: Fifty-one patients were included, with a median age of 66 years (IQR, 56-74) and a male predominance (61%). Most patients (78%) had myeloperoxidase (MPO)-associated AAV. Chronic kidney disease (CKD) was present in 18% of cases, and 96% presented with rapidly progressive glomerulonephritis (RPGN). Hemodialysis was required in 29% of cases. Induction therapy consisted of cyclophosphamide and glucocorticoids in 86%, with a median cyclophosphamide dose of 6 g (IQR, 3.25-8.25). After 2020, five patients received rituximab plus glucocorticoids. Plasma exchange was performed in 12 patients (nine with alveolar hemorrhage). Maintenance therapy included azathioprine in 32 patients and rituximab in six patients. Of patients requiring hemodialysis, 40% recovered kidney function. During follow-up, 39% of patients progressed to end-stage kidney disease, ten patients (20%) relapsed, and 17 died (33%).

Conclusion: This study provides valuable insights into the epidemiology, treatment, and outcomes of AAV with kidney involvement in Portugal. Further studies are needed to optimize treatment strategies across more centers.

Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/complications; Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/drug therapy; Glomerulonephritis; Kidney Diseases

INTRODUCTION

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis that primarily affects small blood vessels and is classically divided into three subtypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1,2] Renal involvement in AAV is indeed a critical factor in determining disease outcomes,[3,4] often leading to kidney failure and requiring specialized treatment approaches. Identifying specific ANCA markers, such as anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO) antibodies, plays an important role in distinguishing between these subtypes and guiding clinical management.[5,6] While AAV with renal involvement is often studied in international cohorts, the clinical characteristics of Portuguese patients with AAV and associated kidney involvement might not be as well-documented in the literature. Given the regional differences in patient presentation, genetic factors, and treatment responses, there may be an underrepresentation of this specific population's outcomes and management approaches.[7-9] This study aims to describe the demographic features, clinical presentation,

Received: 06/02/2025 **Accepted:** 26/05/2025 **Published Online:** 05/06/2025 **Published:** 11/07/2025
* **Corresponding Author:** Adriana Santos | adrianavelososantos@hotmail.com | Alameda Prof. Hernâni Monteiro 4200–319, Porto, Portugal

treatment strategies, and outcomes of a large cohort of AAV patients with kidney involvement managed at our tertiary care center, Hospital de São João.

MATERIAL AND METHODS

Since December 2010, at Hospital de São João in Porto, the ambulatory care of patients with AAV and kidney involvement has been primarily overseen by a multidisciplinary team, comprising two Nephrologists, one Rheumatologist, and one Internal Medicine specialist. This descriptive cross-sectional study identified eligible patients through electronic medical records from January 2010 to June 2023. Inclusion criteria required patients to be aged 18 years or older and have AAV with biopsy-confirmed kidney involvement. Exclusion criteria included serological ANCA--negative cases, eosinophilic granulomatosis with polyangiitis, and overlap syndromes. Data collection focused on demographic and clinical variables, kidney pathology findings, treatment regimens and patient outcomes. The data analysis was performed using SPSS Statistics 27® software.

RESULTS

At the beginning of the study, 80 patients with AAV were assessed for eligibility. As depicted in Fig. 1, 51 patients met the eligibility criteria and were included in the analysis.

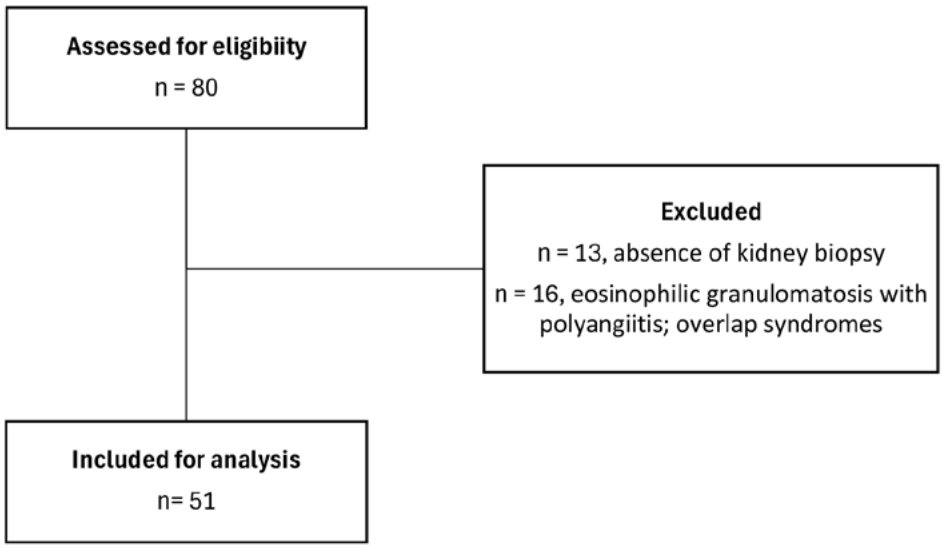

Figure 1. Study flow diagram.

General demographic aspects

A male predominance has been observed in our population, with almost two-thirds of the cohort (n= 31, 61%). At disease presentation, the median age was 66 (IQR, 56-74) years old, and 77% (n= 39) of patients had at least one major comorbidity (hypertension, diabetes, dyslipidemia or overweight/obesity). A previous chronic kidney disease (CKD) diagnosis had been established in 18% (n= 9) of patients before AAV presentation. The median glomerular filtration rate by the CKD-EPI equation was 45 (IQR 35-53) mL/min/1.73 m² in that particular population.

Disease presentation and diagnosis

Only two patients with vasculitic lesions on kidney histology presented with preserved renal function despite microscopic hematuria and proteinuria. Most of our patients (96%, n= 49) had rapidly progressive glomerulonephritis (RPGN) as the renal manifestation of the vasculitic process. The median serum creatinine at disease presentation was 4.2 (IQR, 2.5-5.7) mg/dL and 29% (n= 15) of patients required hemodialysis. According to ANCA specificity, 78% (n= 40) of patients presented a positive test for anti-myeloperoxidase and 22% (n= 11) for anti--proteinase 3 antibodies. Extrarenal manifestations were frequently reported, with involvement of the upper and lower respiratory tract in 43% (n= 22) of cases, the nervous system in 6% (n= 3), the musculoskeletal system in 4% (n= 2), and the eyes in 2% (n= 1). The median diagnosis delay was 30 (IQR, 14-87) days from the onset of the disease to diagnosis, with the majority of delays attributed to delays in referral.

Kidney pathology

According to Berden *et al* histopathologic classification,[10] our patients were classified as having a 'crescentic class', 'mixed class', 'sclerotic class' and 'focal class' presentation in 26 (51%), 15 (29.4%), 5 (9.8%) and 5 (9.8%) cases, respectively. Correlating histologic activity with renal

function at diagnosis, our population was categorized as: low, intermediate or high risk of developing end-stage renal disease (ESRD) in 6 (13.3%), 21 (46.6%) and 18 (40%) cases, respectively, according to renal risk score (RRS) developed by Brix *et al.*[11] Notably, among the evaluated parameters, only the RRS demonstrated a statistically significant correlation with kidney survival (p = 0.003).

Implemented treatment regimens

Concerning "induction" therapy of AAV and according to CYCLOPS study,[12] cyclophosphamide i.v. plus glucocorticoids composed the most used treatment plan, in 44 patients (86%). Rituximab (1 g at weeks 0 and 2) plus glucocorticoids[13] were preferred in five cases (10%), all introduced after 2020 (Fig. 2). In one case (2%) a combination of rituximab (1 g at 0 and 2 weeks) with i.v. cyclophosphamide[14] was used. In one case (2%) no immunosuppressive therapy was initiated due to the presence of massive irreversible lesions documented on kidney biopsy and given the absence of extrarenal manifestations. The median cumulative cyclophosphamide dose was 6 g (IQR, 3.25-8.25). Plasma exchange was performed in 12 cases (24%), nine with alveolar hemorrhage, and all before 2020 (Fig. 2). The median number of sessions per patient was seven. For "maintenance" therapy, azathioprine (AZA) was the standard immunosuppression regimen used in 32 patients (63%). Mycophenolate mofetil (MMF) was used in one case (2%) due to gastrointestinal intolerance to AZA. Maintenance with rituximab was started after 2019 in six cases (12%). The median cumulative dose was 2.5 g (IQR, 2–4). Before the implementation of current guidelines, rituximab was typically selected in cases of azathioprine allergy or intolerance, or in patients with a history of relapse. Glucocorticoid tapering regimens obeyed to the British Society of Rheumatology until 2020 after which a quicker tapering schedule was implemented according to the PEXIVAS study.[15] Representing a median time of 46 (IQR 18 – 100) months on remission maintenance treatment, 31 patients (61%) were under glucocorticoids on the date of the last evaluation (or death or hemodialysis initiation when applicable) with a median daily prednisone dose of 5 mg (IQR 2.5- 5).

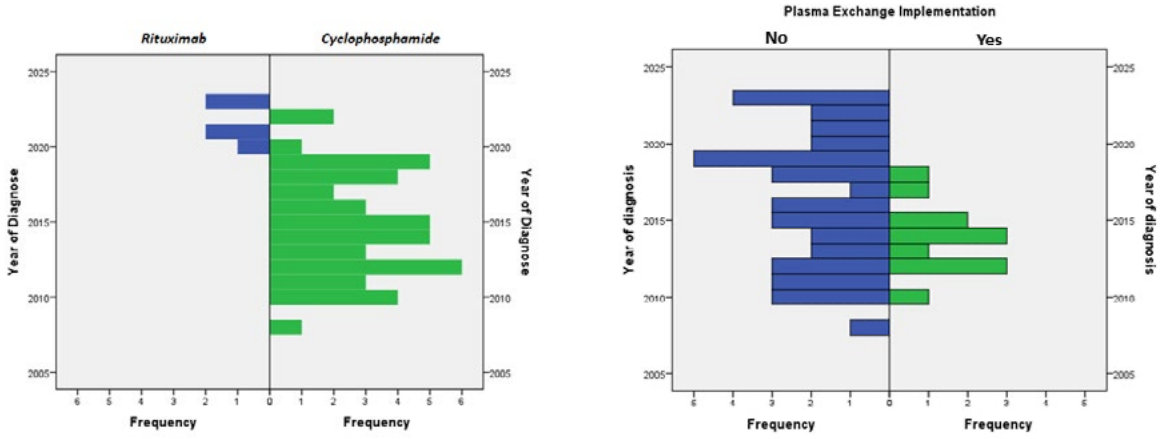

Figure 2. Distribution of "induction" therapy protocols and the implementation of plasma exchange therapies over time in our center.

Outcomes

Of the 15 patients who required hemodialysis at disease presentation, six (40%) presented renal recovery (n= 3 MPO, n= 3 PR3). Nevertheless, during a median follow-up of 39 (IQR, 7-84) months, 20 patients (39%) progressed to end-stage kidney disease, 10 patients (20%) died with preserved renal function and 21 patients (41%) survived with preserved renal function. Relapses occurred in 10 patients (20%), with the respiratory tract being the most frequently involved system (n= 6, 60%). Infection and death affected, respectively, 18 (35%) and 17 patients (33%) during the follow-up period. In patients with a reported cause of death, infectious diseases were the leading cause (29%) followed by cancer (24%) and cardiovascular disease (6%). The median time from AAV diagnosis until death was 67 months (minimum 2 months; maximum 151 months).
Table 1 summarizes the main aspects of the demographic and clinical characteristics of our population.

Table 1. Demographic and clinical characteristics of our population with AAV, according to serologic classification.

	All patients (n = 51)	ANCA – MPO (n = 40)	ANCA-PR3 (n = 11)
Gender			
Male, n (%)	31 (60.8)	26 (65)	5 (45.5)
Female, n (%)	20 (39.2)	14 (35)	6 (54.5)
Age at presentation years (IQR, Q1 – Q3)	66 (56-74)	66 (57-74)	60 (45-74)
Comorbidities			
Hypertension, n (%)	33 (64.7)	30 (75)	3 (27.3)
Diabetes, n (%)	10 (19.6)	8 (20)	2 (18.2)
Type 1	1 (2)	0 (0)	1 (9.1)
Type 2	9 (17.6)	8 (20)	1 (9.1)
Dyslipidemia, n (%)	16 (31.4)	13 (32.5)	3 (27.3)
Overweight/Obesity, n (%)	6 (11.8)	5 (12.5)	1 (9.1)
CKD, n (%)	9 (17.6)	8 (20)	1 (10)
Serum creatinine at disease presentation mg/dL (IQR, Q1 – Q3)	4.2 (2.5-5.7)	4 (2.7-5.6)	4.5 (2.3-6.8)
Requiring dialysis, n (%)	15 (29.4)	11 (27.5)	4 (36.4)
Extrarenal manifestations			
Respiratory system, n (%)	22 (43)	16 (40)	6 (54.5)
Nervous system, n (%)	3 (6)	1 (2.5)	2 (18.2)
Musculoskeletal system, n (%)	2 (4)	1 (2.5)	1 (9)
Eyes, n (%)	1 (2)	0 (0)	1 (9)
Berden histopathologic classification[10]			
Crescentic class, n (%)	26 (51)	19 (47.5)	7 (63.6)
Mixed class, n (%)	15 (29.4)	13 (32.5)	2 (18.2)
Sclerotic class, n (%)	5 (9.8)	3 (7.5)	2 (18.2)
Focal class, n (%)	5 (9.8)	5 (12.5)	0 (0)
Renal risk score[11]			
Low risk, n (%)	6 (13.3)	3 (7.5)	3 (27.3)
Intermediate risk, n (%)	21 (46.6)	16 (40)	5 (45.5)
High risk, n (%)	18 (40)	16 (40)	2 (18.2)
Induction therapy			
Cyclophosphamide plus glucocorticoids, n (%)	44 (86.2)	35 (87.5)	9 (81.8)
Rituximab plus glucocorticoids, n (%)	5 (9.8)	4 (10)	1 (9.1)
Cyclophosphamide plus rituximab, n (%)	1 (2)	0 (0)	1 (9.1)
Plasma exchange, n (%)	12 (23.5)	10 (25)	2 (18.2)
Maintenance therapy			
Azathioprine, n (%)	32 (62.7)	25 (62.5)	7 (63.6)
Rituximab, n (%)	6 (11.8)	3 (7.5)	3 (27.3)
Mycophenolate mofetil, n (%)	1 (2)	1 (2.5)	0 (0)
Renal outcomes*			
Recovery of renal function after dialysis initiation, n (%)	6 (40)	3 (27.3)	3 (75)
Preserved renal function during follow-up, n (%)	21 (41.2)	13 (32.5)	8 (72.7)
Progression to ESKD during follow-up, n (%)	20 (39)	18 (45)	2 (18.2)
Relapses	10 (19.6)	8 (20)	2 (18.2)
Infections	18 (35.3)	16 (40)	2 (18.2)
Mortality	17 (33.3)	15 (37.5)	2 (18.2)

ANCA-MPO: anti-neutrophil cytoplasm antibodies against myeloperoxidase; ANCA-PR3: anti-neutrophil cytoplasm antibodies against proteinase-3; IQR: interquartile range; CKD: chronic kidney disease.
* Censored to death.

DISCUSSION

In a country where epidemiological data on AAV is scarce and needed for a better uniformization of management among clinicians,[16] this is the largest series of patients with biopsy-proven renal AAV reported from Portugal. In line with other Southern European populations,[17,18] our reported mean age at onset of disease was the 6th decade of life, males were the most affected gender and a clear predominance of ANCA-MPO was observed. The majority of patients (77%) had at least one major comorbidity and a significant proportion of patients (18%) had been previously diagnosed with CKD, raising awareness for the high level of suspicion required for the diagnosis of AAV even in comorbid populations. Consistent with other recent literature,[17] our reported 'diagnosis delay' of 1 month follows the idea that time to diagnosis after the occurrence of the first vasculitis-related symptoms is getting shorter in the last decades. Nevertheless, 25% of our patients still have a period between clinical presentation and kidney histopathological confirmation longer than three months. This highlights the importance of not delaying the initiation of immunosuppressive therapy when a clinical presentation is consistent with small-vessel vasculitis and is accompanied by positive ANCA serology, particularly in specialized centers dealing with rapidly deteriorating patients.[19] Kidney biopsy remains crucial for diagnosis confirmation and provides relevant prognostic information.[19] In our population, the MPO subgroup, compared to the PR3 subgroup, exhibited a higher incidence of the mixed class based on the histopathologic classification by Berden *et al*,[10] along with a greater proportion of patients classified as high risk for developing ESRD according to the Renal Risk Score proposed by Brix *et al*.[11] This aligns with the observation that the PR3 subgroup experienced a higher rate of renal function recovery after dialysis initiation and better preservation of kidney function during follow-up. Notably, in our cohort, the RRS was the only available tool for predicting kidney survival.[20] Regarding induction treatment protocol, our department's practice began to change around 2020s. After gaining an on-label indication for AAV,[13] rituximab has become available as a biosimilar, which simplified its prescription. As such, in the past years, we have experienced a progressive switch from cyclophosphamide to rituximab as the first-line drug for the treatment of AAV, especially in older and frail patients. Based on the findings of recent randomized controlled trials,[13,14,22] we believe that larger and more rigorous studies will be crucial in supporting the broader adoption of treatment regimens designed to minimize drug-related toxicity. In accordance with the best available evidence, our department has progressively implemented protocols involving more rapid glucocorticoid tapering over the years.[15] The PEXIVAS study[15] has guided our clinical approach to the use of plasmapheresis in AAV. Nonetheless, accumulating evidence supports considering plasma exchange in patients who present with dialysis-dependent kidney injury or rapidly progressive renal dysfunction. If it is true that since the 1960s a dramatic improvement in AAV therapeutic arms and prognosis was observed with oral cyclophosphamide and glucocorticoid,[21] nowadays we still notice a 39% progression to end-stage kidney disease during a median follow-up of 39 months in our population. Mortality reaches 33%, mostly due to infectious or unknown causes, and the infection rate gets 35% of our patients. This reality, combined with the limited evidence supporting the use of rituximab in patients with significantly reduced or rapidly declining glomerular filtration rates,[14] highlights the need for a more tailored approach for the Portuguese population.[16] In summary, this study is a modest but important cohort of Portuguese patients with renal AAV. Despite some limitations, like the descriptive and retrospective design of the study, recruitment from the same geographical zone (North of Portugal), and absence of information about cumulative dose of glucocorticoids, we believe this paper offers an important representation of the epidemiology, diagnosis, treatment regimens, and outcomes of ANCA-positive vasculitis patients with kidney involvement in Portugal. Fortunately, in recent years, multicenter initiatives and national registries have been established by the Immunonephrology Working Group of the Portuguese Society of Nephrology. These efforts aim to provide a more comprehensive understanding of small-vessel vasculitis within our country.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

Contributorship Statement

AS: Bibliographical search, data collection, analysis and interpretation of results, drafting the article, critical reviewing of the content of the article.
NP: A drafting of the article, data collection, critical reviewing of the content of the article.
NM, RF: Data collection.
AP: Analysis and interpretation of results.
EP, EV, RN, IF: Critical reviewing of the content of the article.
All authors approved the final version to be published.

REFERENCES

1. Fries JF, Hunder GG, Bloch DA, Michel BA, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum. 1990;33:1135-6.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1-11.
3. Sinico RA, Di Toma L, Radice A. Renal involvement in anti-neutrophil cytoplasmic autoantibody associated vasculitis. Autoimmun Rev. 2013;12:477-82. oi: 10.1016/j.autrev.2012.08.006.
4. Solans-Laqué R, Fraile G, Rodriguez-Carballeira M, Caminal L, Castillo MJ, Martínez-Valle F, et al. Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity. Medicine. 2017;96:e6083. doi: 10.1097/MD.0000000000006083.
5. Robson JC, Grayson PC, Ponte C, Suppiah R, Craven A, Judge A, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81:315-20. doi: 10.1136/annrheumdis-2021-221795.
6. Suppiah R, Robson JC, Grayson PC, Ponte C, Craven A, Khalid S, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. Ann Rheum Dis. 2022;81:321-6. doi: 10.1136/annrheumdis-2021-221796.
7. Domingues VM, Machado B, Santos J. ANCA-positive vasculitis: Clinical implications of ANCA types and titers. Rev Assoc Med Bras. 2016;62:434-40. doi: 10.1590/1806-9282.62.05.434.
8. Ponte C, Khmelinskii N, Teixeira V, Luz K, Peixoto D, Rodrigues M, et al. Reuma.pt/vasculitis - the Portuguese vasculitis registry. Orphanet J Rare Dis. 2020;15:110. doi: 10.1186/s13023-020-01381-0.
9. Fonseca JA, Gameiro J, Duarte I, Jorge S, Lopes JA. The neutrophil-to-lymphocyte ratio as a marker of vasculitis activity, severe infection and mortality in ANCA-associated vasculitis: A retrospective study. Nefrologia. 2021;41:321-8. doi: 10.1016/j.nefroe.2021.07.005.
10. Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol. 2010;21:1628-36. doi: 10.1681/ASN.2010050477.
11. Brix SR, Noriega M, Tennstedt P, Vettorazzi E, Busch M, Nitschke M, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. Kidney Int. 2018;94:1177-88. doi: 10.1016/j.kint.2018.07.020.
12. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis. 2012;71:955-60. doi: 10.1136/annrheumdis-2011-200477.
13. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221-32. doi: 10.1056/NEJMoa0909905.
14. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211-20.
15. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382:622-31. doi: 10.1056/NEJMoa1803537.
16. Ferreira I, Águeda A, Belino C, Schau B, Rovisco J, Ferreira C. Insights from Portuguese Nephrologists and Rheumatologists Concerning the Treatment of ANCA Vasculitis. Acta Med Port. 2024;37:778-86. doi: 10.20344/amp.21635.
17. Mohammad AJ. An update on the epidemiology of ANCA-associated vasculitis. Rheumatology. 2020;59:iii42-iii50.
18. Pearce FA, Craven A, Merkel PA, Luqmani RA, Watts RA. Global ethnic and geographic differences in the clinical presentations of anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology. 2017;56:1962-9. doi: 10.1093/rheumatology/kex293.
19. KDIGO 2024 Clinical Practice Guideline for the Management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Kidney Int. 2024;105:S71-s116. doi: 10.1016/j.kint.2023.10.008.
20. Santos A, Figueiredo R, Paulo N, Marques N, Pereira E, Mariz E, et al. #675 Application of ANCA-associated vasculitis Histopathological Classification and Renal Risk Score for prediction of end-stage kidney disease. Nephrol Dial Transplant. 2024;39: gfae069-0334-675. doi: 10.1093/ndt/gfae069.334.
21. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med. 1983;98:76-85. doi: 10.7326/0003-4819-98-1-76.
22. Jayne DR, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med. 2021;384:599-609. doi: 10.1056/NEJMoa2023386. Erratum in: N Engl J Med. 2024;390:388. doi: 10.1056/NEJMx230010.