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Insights from Portuguese Nephrologists and Rheumatologists Concerning the Treatment of ANCA Vasculitis

Perspetivas dos Nefrologistas e Reumatologistas Portugueses Sobre o Tratamento das Vasculites Associadas aos ANCA

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ABSTRACT

Introduction: Antineutrophilic cytoplasmic antibodies-associated vasculitis (AAV) encompasses granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. These rare diseases are characterized by an exaggerated immune response in blood vessels, leading to inflammation, vascular injury, ischemia, and necrosis of affected tissues and organs. Despite the existence of European recommendations for treating AAV, their implementation in Portugal remains unclear.

Methods: To address this gap, an online Delphi panel was conducted involving 55 Portuguese nephrologists and rheumatologists, representing the main specialties involved in the management of AAV. The primary objective was to assess the level of consensus regarding the treatment of AAV in Portugal and the application of European recommendations in daily clinical practice. The specialists evaluated 29 statements formulated by a group of Portuguese experts with extensive experience in AAV, addressing key aspects of AAV management, rated on a 4-point Likert scale. Consensus was defined as > 70% of responses either strongly agreeing or strongly disagreeing with a statement, while the majority level required > 70% agreement or disagreement.

Results: After one round, no statement reached consensus globally, and eight out of the 29 statements did not achieve a qualified majority. Nonetheless, this study demonstrates a high level of agreement within each medical specialty, due to the distinct characteristics of the patient populations treated by each specialty. While the results suggest partial adherence to European recommendations, they also highlight the need to standardize clinical practices for AAV treatment in Portugal.

Conclusion: This study underscores the importance of aligning national practices with established European recommendations to ensure the best outcomes for patients with AAV.

Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/drug therapy; Nephrologists; Practice Patterns, Physicians; Rheumatologists

RESUMO

Introdução: As vasculites associadas a anticorpos citoplasmáticos antineutrófilos (AAV) engloba a granulomatose com poliangiite, a poliangiite microscópica e a granulomatose eosinofílica com poliangiite. Estas doenças raras caracterizam-se por uma resposta imunológica exacerbada nos vasos sanguíneos, levando a inflamação, lesão vascular, isquemia e necrose dos tecidos e órgãos afetados. Apesar de existirem recomendações europeias para o tratamento da AAV, a sua implementação em Portugal permanece desconhecida.

Métodos: Para abordar esta lacuna, foi realizado um painel *online* do tipo Delphi envolvendo 55 nefrologistas e reumatologistas portugueses, representando as principais especialidades envolvidas na gestão da AAV. O principal objetivo foi avaliar o nível de consenso em relação ao tratamento da AAV em Portugal e aplicação das recomendações europeias na prática clínica diária. Os especialistas avaliaram 29 afirmações formuladas por um grupo de peritos portugueses com vasta experiência em AAV, abordando aspetos-chave da gestão da AAV, classificadas numa escala Likert de 4 pontos. O consenso foi definido como > 70% das respostas a concordar totalmente ou a discordar totalmente com uma declaração, enquanto o nível de maioria exigia > 70% de concordância ou discordância.

Resultados: Após uma ronda, nenhuma declaração alcançou consenso de forma global, e oito das 29 declarações não atingiram uma maioria qualificada. Contudo, este estudo demonstra um elevado nível de concordância em cada especialidade médica, devido às características distintas das populações de doentes tratadas por cada especialidade. Embora os resultados sugiram uma adesão parcial às recomendações europeias, também destacam a necessidade de padronizar as práticas clínicas de tratamento da AAV em Portugal.

Conclusão: Este estudo sublinha a importância de alinhar as práticas nacionais com as recomendações europeias estabelecidas para garantir os melhores resultados para os doentes com AAV.

Palavras-chave: Nefrologistas; Padrões de Prática Médica; Reumatologistas; Vasculite Associada a Anticorpo Anticitoplasma de Neutrófilos

INTRODUCTION

Antineutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of rare diseases consisting of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1,2] Its estimated incidence is 10 to 20 new cases per million individuals per year in Europe and a prevalence rate of 46 to 184 per million individuals.[3,4]

The pathogenic role of ANCA results from the induction of an exacerbated immune response in blood vessels, leading to inflammation, vascular injury, ischemia, and necrosis

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of the affected tissues and organs.[5,6] Vasculitis management, namely disease activity status, and cumulative impact on patient's health can be performed using the Birmingham Vasculitis Activity Score (BVAS) and the Vascular Damage Index (VDI), respectively.[7-11] Following AAV diagnosis, the immunosuppressive regimen used to treat this condition should be promptly initiated, as a delay in treatment initiation leads to a worse prognosis.[12] Recently, the European League Against Rheumatism/ European Renal Association-European Dialysis and Transplant Association (EULAR/ ERA-EDTA) published guidelines for the two phases of AAV treatment[12-15]: The remission induction phase (a more aggressive immunosuppression phase to achieve remission in three months, defined by the complete absence of signs

Table 1 – Defined statements for the Delphi-like panel

A. Therapeutic scheme	
1	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is cyclophosphamide, associated with corticotherapy.
2	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is rituximab, associated with corticotherapy.
3	I prescribe a rapid weaning scheme for oral corticotherapy according to the PEXIVAS scheme.
4	The treatment of ANCA vasculitis is independent of the type of antibody.
5	The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy.
6	The immunosuppressant I most often prescribe in maintenance therapy is methotrexate and corticotherapy.
7	The immunosuppressant I most often prescribe in maintenance therapy is rituximab and corticotherapy.
8	In severe disease in remission, I suspend maintenance therapy after 18 months.
9	In severe disease in remission, I do not suspend corticotherapy.
10	The use of avacopan in ANCA vasculitis minimizes the use of corticotherapy.
11	The use of avacopan in ANCA vasculitis has been tested and can be used in induction schemes.
12	Avacopan may be helpful in corticodependent cases and may be considered for maintenance of remission in combination with another immunosuppressant.
13	Avacopan is equally effective in granulomatous as in non-granulomatous manifestations.
14	Avacopan is a therapeutic alternative to corticosteroids in the treatment of ANCA vasculitis.
B. Refractory and/or relapsing disease	
15	I change the induction immunosuppressive regimen when treating relapse.
16	I repeat the renal biopsy on suspicion of renal recurrence.
17	IVIg can be used in refractory cases and when the risk of infection is high.
C. Renal disease	
18	I perform renal biopsy whenever renal involvement by ANCA vasculitis is suspected.
19	Renal failure usually precludes the use of methotrexate.
20	Plasmapheresis still has a place in the treatment of ANCA vasculitis with renal involvement.
D. Other manifestations of illness and/or comorbidities	
21	Immunosuppression, namely high-dose corticotherapy, is the first-line treatment for orbital pseudotumor.
E. Safety	
22	Low-dose corticotherapy has a good long-term safety profile and is virtually risk-free.
F. Prophylaxis	
23	I do prophylaxis for *Pneumocystis jirovecii* with cotrimoxazole.
24	I do prophylaxis for fungal infections.
25	I do prophylaxis for osteoporosis.
26	I screen for tuberculosis before starting immunosuppression.
27	I assess the risk of reactivation of hepatitis B in patients treated with RTX.
G. Monitoring and follow-up	
28	I use the BVAS/VDI for therapeutic decisions and/or disease activity monitoring.
29	I use FFS for therapeutic decisions.

of active disease),[16] and the maintenance phase (less intense phase, aimed at maintaining remission and minimizing medication-related adverse effects).[6,13,17] In patients with generalized or severe-stage disease (renal failure with creatinine > 5.65 mg/dL or significant organ changes, such as pulmonary hemorrhage), the first-line therapy is based preferably on rituximab (RTX), or on cyclophosphamide (CYC).[12]

Considering the inherent toxicity of corticosteroid-based regimens, other effective alternatives have been under evaluation, such as avacopan.[6] Avacopan is an oral inhibitor of the C5a complement receptor, which prevents complement-mediated activation and migration of pro-inflammatory leukocytes.[18,19] This new compound showed superiority in maintaining remission at 52 weeks and reduced the relapse rate from 21% to 10% compared to a prednisone regimen in gradual dose reduction for 20 weeks (phase III ADVOCATE study).[19] Avacopan effectively contributed to remission in relapses and severe disease, while breaking through steroid dependency and allowing corticosteroid tapering.[20,21] Given its high potential as a therapeutic alternative to corticosteroids, the use of avacopan in the treatment of AAV has been added to the official 2023 EULAR revision and Canadian recommendations.[14,22,23]

Although knowledge about these diseases is constantly evolving, the recommendations of specialists should be the mainstay of medical decision-making, always framed by the specific context of each patient and their circumstances. Despite the existence of European recommendations for treating AAV,[12,13,15,24] their implementation in the Portuguese reality is not known. Therefore, this Delphi-like panel assessed the positioning of national nephrology and rheumatology specialists regarding the treatment of AAV in Portugal, in order to raise awareness on the need to standardize clinical procedures across the Portuguese healthcare context.

METHODS

This study assessed the agreement of nephrology and rheumatology specialists on clinical practice methodologies regarding AAV treatment.

To accomplish it, five Portuguese experts in ANCA vasculitis joined a focus group and formulated 29 statements based both on evidence-based clinical practice and on the EULAR recommendations for the management of ANCA-associated vasculitis.[14] The topics covered included the therapeutic scheme, refractory and/ or relapsing disease, renal disease, other manifestations of illness and/ or comorbidities, safety, prophylaxis and monitoring, and follow-up (Table 1). Following the focus group, a Delphi-like panel of only one round was conducted (Fig. 1). A group of 113 national nephrologists and rheumatologists was invited to anonymously answer the questionnaire, and to categorize the previously defined 29 statements using a 4-point Likert scale: “fully disagree”, “disagree”, “agree”, and “fully agree”. The consensus agreement level was set according to the definitions described in Fig. 1. The responses were analyzed by the frequency distribution through the presented 4-point Likert scale.

RESULTS

This one-round Delphi-like panel included 34 nephrologists and 21 rheumatologists (a total of 55 individuals), from a universe of 113 invited clinicians, who were requested to categorize the 29 statements elaborated by the focus group using a 4-point Likert scale. The results were analyzed considering all the responses and according to the medical specialty (Table 2).

No statement was categorized as consensual regarding the total number of responses (Table 2). A qualified majority was obtained in 21 statements, with more than 70% of the collective agreement (“fully agree” and “agree”) in 16 statements, and more than 70% of the collective disagreement (“fully disagree” and “disagree”) in the five remaining ones (Table 2). The lasting eight statements attained heterogeneous answers (Table 2 and Fig. 2). The highest level of discrepancies was obtained for the following statements: “The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy” (therapeutic scheme), “I do prophylaxis for fungal infections” (prophylaxis), and “I use (Five Factor Score) FFS for therapeutic decisions” (monitoring and follow-up).

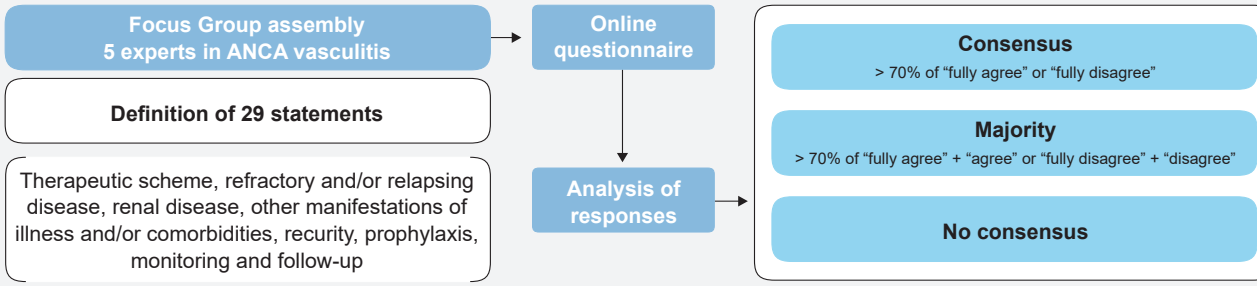

Figure 1 – Methodology of the Delphi-like panel (one round only)

Table 2 – Statements defined for the Delphi panel. In light green, the statements where a majority was obtained among all experts (> 70% of "fully agree" + "agree" = "Agreed"); in orange, the statements where a majority was obtained among all experts (> 70% of "fully disagree" + "disagree" = "Disagreed"); in dark green/red, the statements where consensus was identified (agree/disagree); in grey, statements were no consensus or qualified majority was gathered.

	A. Therapeutic scheme	Total	N	R
1	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is cyclophosphamide, associated with corticotherapy.	74%	85%	
2	In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is rituximab, associated with corticotherapy.			100%
3	I prescribe a quick weaning scheme for oral corticotherapy according to the PEXIVAS scheme.	86%	97%	
4	The treatment of ANCA vasculitis is independent of the type of antibody.	71%	74%	
5	The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy.			
6	The immunosuppressant I most often prescribe in maintenance therapy is methotrexate and corticotherapy.	87%	C	
7	The immunosuppressant I most often prescribe in maintenance therapy is rituximab and corticotherapy.			71%
8	In severe disease in remission, I suspend maintenance therapy after 18 months.	71%		86%
9	In severe disease in remission, I do not suspend corticotherapy.	82%	76%	91%
10	The use of avacopan in ANCA vasculitis minimizes the use of corticotherapy.	100%	100%	100%
11	The use of avacopan in ANCA vasculitis has been tested and can be used in induction schemes.	76%	71%	86%
12	Avacopan may be helpful in corticodependent cases and may be considered for maintenance of remission in combination with another immunosuppressant.	95%	94%	95%
13	Avacopan is equally effective in granulomatous as in non-granulomatous manifestations.	76%	74%	81%
14	Avacopan is a therapeutic alternative to corticosteroids in the treatment of ANCA vasculitis.	89%	91%	86%
	B. Refractory and/or relapsing disease			
15	I change the induction immunosuppressive regimen when treating relapse.	75%	74%	76%
16	I repeat the renal biopsy on suspicion of renal recurrence.			
17	IVIg can be used in refractory cases and when the risk of infection is high.	83%	74%	100%
	C. Renal disease			
18	I perform renal biopsy whenever renal involvement by ANCA vasculitis is suspected.	84%	85%	81%
19	Renal failure usually precludes the use of methotrexate.	78%	94%	
20	Plasmapheresis still has a place in the treatment of ANCA vasculitis with renal involvement.			76%
	D. Other manifestations of illness and/or comorbidities			
21	Immunosuppression, namely high-dose corticotherapy, is the first-line treatment for orbital pseudotumor.	84%	88%	76%
	E. Safety			
22	Low-dose corticotherapy has a good long-term safety profile and is virtually risk-free.	93%	94%	90%
	F. Prophylaxis			
23	I do prophylaxis for *Pneumocystis jirovecii* with cotrimoxazole.	96%	100%	91%
24	I do prophylaxis for fungal infections.		73%	76%
25	I do prophylaxis for osteoporosis.	98%	97%	C
26	I screen for tuberculosis before starting immunosuppression.	91%	91%	91%
27	I assess the risk of reactivation of hepatitis B in patients treated with RTX.	98%	97%	C
	G. Monitoring and follow-up			
28	I use the BVAS/VDI for therapeutic decisions and/or disease activity monitoring.			86%
29	I use FFS for therapeutic decisions.			

Total: combined responses (%) in terms of agreement/disagreement, considering all specialties (n = 55); N: combined responses (%) in terms of agreement/disagreement, considering only nephrology (n = 34); R: combined responses (%) in terms of agreement/disagreement, considering only rheumatology (n = 21).
ANCA: antineutrophilic cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; C: consensus; FFS: five factor score; IVIg: intravenous immunoglobulins; RTX: rituximab; VDI: vascular damage index.

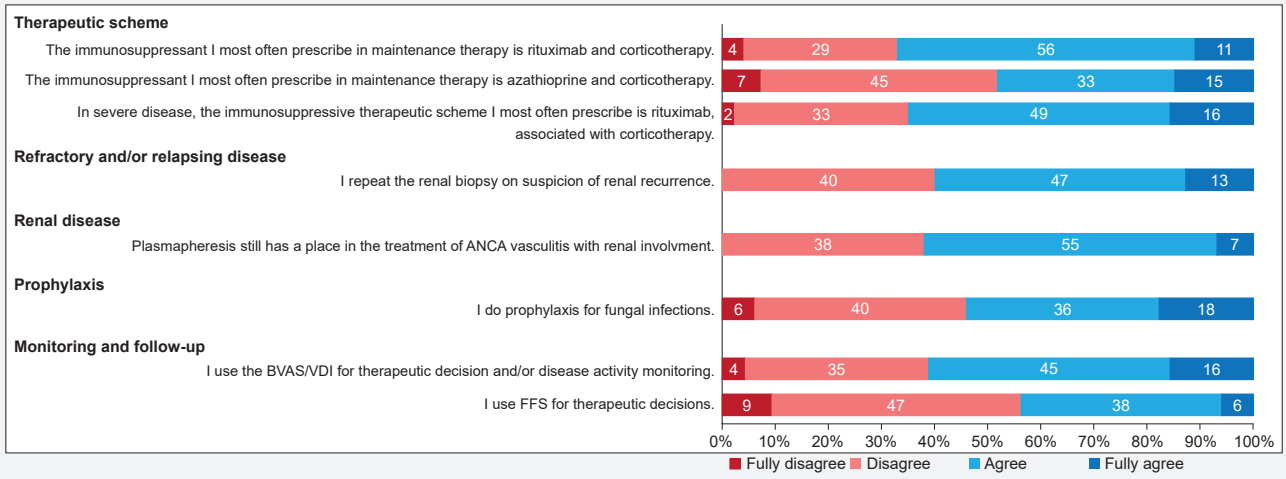

Figure 2 – Characterization of the statements (per %) that failed to achieve a qualified majority after the Delphi-like panel

The analysis of the results per specialty disclosed a marginally increased agreement compared to the overall analysis. Regarding nephrology, a consensus was obtained in one statement from the 'therapeutic scheme' section, specifically the full disagreement with the sentence "The immunosuppressant that I most often prescribe in maintenance therapy is methotrexate and corticotherapy" (statement six, Table 2). A qualified majority was obtained in 20 statements (17 expressing agreement and three stating disagreement, Table 2), and in the remaining eight, the answers received were heterogeneous (Table 2 and Fig. 3). Among these, in the 'therapeutic scheme' section, the two statements with higher response variability were "The immunosuppressant I most often prescribe in maintenance therapy is azathioprine and corticotherapy" and "The immunosuppressant I most often prescribe in maintenance therapy is rituximab and corticotherapy"; and in the Monitoring and Follow-up section were "I use the BVAS/VDI for therapeutic decision and/or disease activity monitoring" and "I use FFS for therapeutic decisions". Interestingly, in the 'renal disease' section, the statement "Plasmapheresis still has a place in the treatment of ANCA vasculitis with renal involvement" divided the experts' opinions almost evenly (nearly 50% agreed and 50% disagreed).

The highest level of agreement registered in this Delphi-like panel was obtained in the rheumatology panel. Specifically, a consensus was obtained in two statements from the 'prophylaxis' section, specifically, "I perform osteoporosis prophylaxis" (statement 25) and "I evaluate the risk of reactivation of hepatitis B in patients treated with RTX" (statement 27, Table 2). A qualified majority was obtained in 19 statements (15 expressing agreement and 4 stating

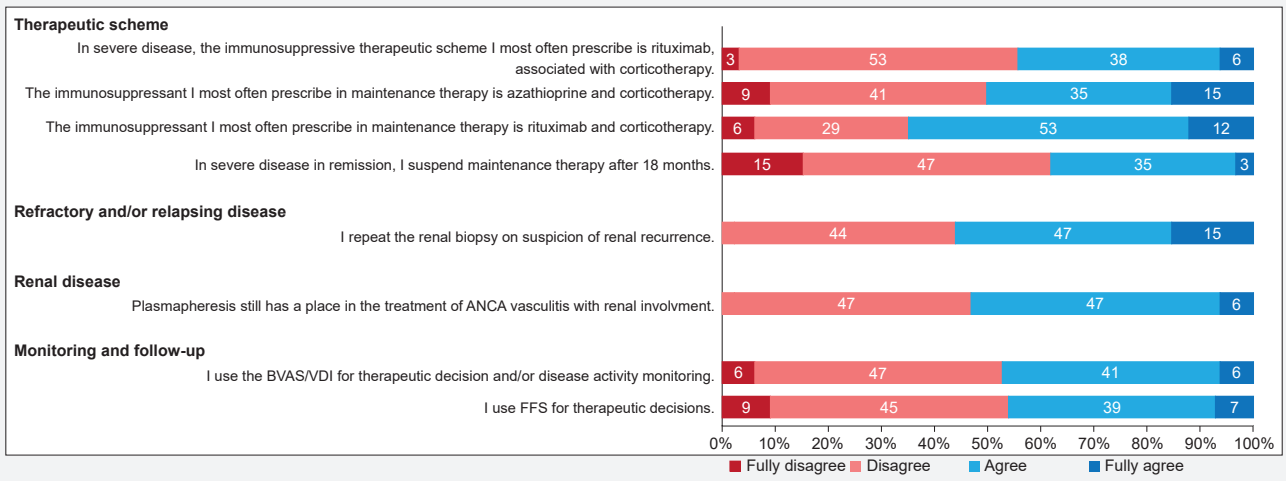

Figure 3 – Characterization of the statements (per %) that failed to achieve a qualified majority after the Delphi-like panel among the nephrologists

disagreement, Table 2). In the remaining eight, the answers were heterogeneous (Table 2 and Fig. 4). Specifically, the statements "In severe disease, the immunosuppressive therapeutic scheme I most often prescribe is cyclophosphamide, associated with corticotherapy" (therapeutic scheme) and "Renal failure usually precludes the use of methotrexate" (renal disease) are those that obtained more pronounced divergence.

DISCUSSION

This Delphi-like panel assessed the positioning of national nephrology and rheumatology specialists regarding the treatment of AAV in Portugal. Despite the existence of various international recommendations for the therapeutic management of AAV, these might not be feasible to use in clinical practice, affecting the patients' proper diagnosis, treatment, and prognosis. Therefore, generating knowledge and unifying opinions is essential to come up with the most suitable and personalized therapeutic scenario to improve these patients' QoL. The outcome of this panel of experts was in adequate compliance with European recommendations for managing these diseases. Still, the overall analysis revealed a high lack of consensus regarding the treatment of AAV patients among different specialties.

In the 'therapeutic scheme' section, explicitly referring to the most prescribed immunosuppressive therapeutic scheme in severe disease, most experts advocate for a combination of CYC and corticosteroids. Notably, this recommendation is more aligned with nephrologists, whereas rheumatologists seem to prefer RTX with corticosteroids. This divergence in approach may stem from the distinctive medical responsibilities, with nephrologists typically managing cases involving significant renal complications. Moreover, the available data regarding the use of RTX and corticosteroids in induction therapy for patients with notably reduced or rapidly declining glomerular filtration rates (GFR), especially those with a serum creatinine level exceeding 4 mg/dL (354 µmol/L), is limited, thus favoring CYC as the preferred agent for inducing remission in cases of severe kidney disease. Despite the association of CYC with infertility, due to young patients' exposure to gonadal toxicity and an elevated risk of cancer development, its combined use with corticosteroids has been the only available option for many years, and it is recognized as a valuable therapeutic strategy.[12,25,26] Following remission, most rheumatologists agreed to use RTX combined with corticosteroids for maintenance therapy,[27-29] a practice endorsed by the EULAR/EDTA guidelines,[12,14] instead of MTX or AZA. Nephrologists also consensually disagreed with MTX due to its nephrotoxic potential, dose adjustments needed due to chronic kidney disease (CKD), and lack of indication during dialysis, thus favoring alternative maintenance regimens. Specifically, there is evidence that suggests that RTX may offer advantages, particularly for patients with a history of relapsing disease, proteinase 3-ANCA (PR3)-positive AAV, AZA intolerance and following RTX induction. Still, it is essential to exercise caution, as long-term data on the effects of RTX maintenance therapy are limited, with potential concerns regarding the development of secondary immunodeficiency in this patient population.

Concerning the tapering of oral corticosteroids, the consensus among experts leans towards adopting the PEXIVAS trial protocol.[30] The analysis according to medical specialty shows that this inclination is primarily driven by nephrologists, with 33% of rheumatologists expressing disagreement with its adoption. The PEXIVAS scheme was

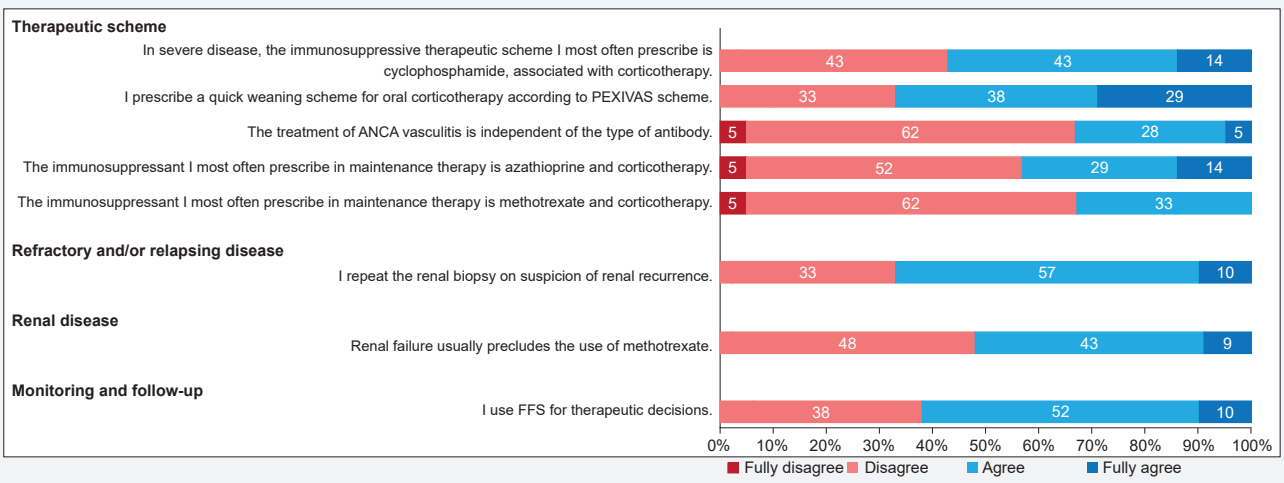

Figure 4 – Characterization of the statements (per %) that failed to achieve a qualified majority after the Delphi-like panel among the rheumatologists

evaluated in a recent randomized clinical trial, specifically assessing the role of PLEX (plasma exchange) and two corticosteroid regimens (standard and reduced dose) in patients with severe AAV [estimated GFR < 50 mL/min/1.73 m^2 of body-surface area, or diffuse alveolar hemorrhage (DAH)]. This study found that the reduced-corticosteroid regimen was non-inferior to a standard dose concerning death and end-stage renal disease (ESRD) outcomes, while it significantly reduced the risk of severe infections within the first year of treatment.[30]

Notably, efforts are being made to reduce the toxicity associated with high-dose, prolonged corticosteroid regimens, particularly in frail patients, due to toxicity and side effects.[31] Accordingly, most experts disagreed on not suspending corticosteroids in severe disease in remission. The recent appraisal of pathogenetic mechanisms, including complement activation pathways, has introduced the concept of an alternative to corticosteroids, such as avacopan.[32] Therefore, the final topic of this section focused on avacopan, and most experts agreed that its usage could be adopted in induction schemes, allowing the reduction of corticosteroids and being equally effective in granulomatous and non-granulomatous manifestations. Most experts agree that avacopan is a suitable therapeutic alternative to corticosteroids in treating ANCA vasculitis, which aligns with the EULAR recommendations for managing AAV.[14]

In the 'refractory and/or relapsed disease' section, the overall analysis of the responses reflects those from each specialty. Most experts agree that the immunosuppression regimen should be altered when treating a relapse. In fact, alternative approaches beyond a temporary corticosteroid dosage increase should be used, not only because disease activity is often less severe at relapse than at initial diagnosis but also considering patients with frequent relapses.[33] One available option for refractory or relapsing disease endorsed by most experts, and when the risk of infection is high, is intravenous immunoglobulins (IVIg). This option is usually considered in patients with hypogammaglobulinemia, especially with recurrent infections, either as Ig replacement therapy or in addition to ongoing immunosuppression.[34,35] A recent meta-analysis explored the role of IVIg in active AAV and disclosed that BVAS significantly decreased after the administration.[36]

There was no agreement on the prospect of repeating renal biopsy in cases where renal recurrence is suspected, primarily due to the invasiveness of the procedure and associated risks, with some experts arguing that clinical and immunological assessments may suffice for diagnosing recurrence. Still, the EULAR task force recommends biopsies to evaluate further patients suspected of relapsing vasculitis.[14]

In the 'renal disease' section, most experts agreed to perform a renal biopsy whenever renal involvement by AAV is suspected. Renal involvement usually leads to ESRD and increases mortality. Prompt diagnosis and initiation of adequate immunosuppressive therapy are critical to ensure the best patient and kidney outcomes.[37] Most nephrologists agreed that MTX is contraindicated in renal failure, emphasizing their primary role in treating patients with severe renal involvement. On the other hand, rheumatologists frequently employed MTX as an immunosuppressive agent in their practice. Still, caution is warranted, particularly in cases of ANCA vasculitis, as there is a recognized risk of adverse events, and dose adjustments are recommended for patients with renal impairment.

Regarding plasmapheresis, most rheumatologists consider that this intervention still has a place in treating ANCA vasculitis. In contrast, while acknowledging its utility in severe cases, nephrologists are influenced by the PEXIVAS trial findings, which demonstrated limited benefits in moderate circumstances. Specifically, it failed to establish a significant delay in kidney failure or mortality with plasma exchange in patients with AAV, particularly those with reduced kidney function or alveolar hemorrhage, over a median follow-up period of 2.9 years.[30]

In the 'other manifestations of illness and/ or comorbidities' section, most experts agreed that immunosuppression is the first-line treatment for orbital pseudotumor, probably related to their availability and efficacy in inducing disease remission.[38] Unsurprisingly, most experts disagreed that low dose corticosteroids have a good long-term safety profile, being virtually risk-free, concerning the 'safety' section.

In the 'prophylaxis' section, most experts from both medical specialties agreed to perform prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) with cotrimoxazole and osteoporosis scenarios (consensus in rheumatology), which aligns with the EULAR recommendations. Notably, while most nephrologists agreed to perform prophylaxis for fungal infections, rheumatologists advocated the opposite, which stems from their distinct patient populations. Nephrologists typically manage severely ill and highly immunosuppressed patients, often dealing with CKD cases. Therefore, they commonly recommend prophylaxis for fungal infections using agents like nystatin, akin to post-renal transplantation care. This approach acknowledges the added immunosuppressive impact of CKD and azotemia. Conversely, rheumatologists adopt a different approach, refraining from advocating for fungal infection prophylaxis, mainly because invasive fungal infections are infrequent in AAV patients.[39] The experts also agreed to screen for tuberculosis before starting immunosuppression and to assess the risk of reactivation of hepatitis B in patients treated with RTX (consensus in rheumatology), considering that infection is the most significant contributor to morbidity and mortality in the first

year of treatment.[39]

Finally, in the 'monitoring and follow-up' section, the answers reflected a more heterogeneous practice. Most rheumatologists agreed to adopt the BVAS/VDI for therapeutic decisions and/or disease activity monitoring, and no agreement was reached when considering the FFS for the therapeutic decision, possibly due to the challenging assessment of its utility in clinical practice. Nonetheless, it is advisable to do a comprehensive clinical evaluation during follow-up examinations at regular intervals, as AAV impacts several organs and relapses are common. The BVAS can be helpful in methodically documenting treatment responses in clinical practice. To prevent unnecessary intensified treatment, it is essential to distinguish between damage caused by AAV or its treatment and actual disease.

This study has several limitations that warrant consideration. One significant limitation is the representativeness of the panel, which comprised 34 nephrologists and 21 rheumatologists. While this panel included experts from two relevant specialties, the imbalance in the number of nephrologists compared to rheumatologists may have influenced the consensus, potentially skewing the results towards nephrological perspectives on AAV treatment. Moreover, the severity of AAV patients followed by nephrologists and rheumatologists differs intrinsically. Expert participation in the Delphi survey was by invitation and voluntary, potentially attracting those with a particular interest in AAV. The inclusion of immunologists or general internists would have also provided a more holistic view of AAV management, due to their role in the management of these patients. Furthermore, geographic and practice setting diversity within the panel can also impact the generalizability of the findings across different patient populations within the Portuguese healthcare scenario. Further research is essential to confirm the findings. A Portuguese multicenter trial would be crucial to better understand the patient population, treatment protocols, and clinical outcomes. Additionally, it would provide clear differentiation of results across various procedures.

CONCLUSION

This study represents, to the best of our knowledge, the first assessment of consensus levels concerning the treatment of AAV in Portugal and the integration of European recommendations into daily clinical practice. This study demonstrates a high level of agreement within each medical specialty (nephrology and rheumatology), attributable to the unique characteristics of the patient populations they manage. Concerns regarding the safety implications of long-term corticosteroids are shared by both rheumatologists and nephrologists. There was also a noteworthy consensus on the prophylactic treatment for opportunistic infections and unanimous support for the use of avacopan. These findings underscore the critical need for initiatives aimed at enhancing awareness and education among Portuguese physicians regarding disease monitoring scores. Lastly, this study underscores the importance of aligning national practices with established European recommendations to ensure the best outcomes for patients with AAV.

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AUTHOR CONTRIBUTIONS

IF, AA; CB, JR, CF: Study design, writing and critical review of the manuscript, approval of the final version of the paper.

BS: Approval of the final version of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

IF received honoraria for lectures from CSL Vifor and GlaxonSmithKline, and support for attending congresses from CSL Vifor.

AA received honoraria for lectures from CSL Vifor and Amgen.

CB received honoraria for lectures from CSL Vifor.

BS is an employee of CSL Vifor.

JR received honoraria for advisory boards from CSL Vifor.

CF received honoraria for lectures and support for attending congresses from CSL Vifor and AstraZeneca.

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